OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

Memorandum

SUBJECT: Transmittal of Meeting Minutes and Final Report for the TSCA Science Advisory
           Committee on Chemicals Methylene Chloride Meeting held December 3-4, 2019

TO: Mark Hartman
           Acting Director
           Office of Pollution, Prevention and Toxics

FROM: Todd Peterson, PhD   *Todd Peterson 3/2/2020*
           Designated Federal Official
           TSCA Science Advisory Committee on Chemicals
           Office of Science Coordination and Policy

THRU: Steven Knott, MS   *Steven Knott 3/2/2020*
           Executive Secretary
           TSCA Science Advisory Committee on Chemicals
           Office of Science Coordination and Policy

           Hayley Hughes, DrPH, MPH, CSP   *Barry W. B... for 3/2/2020*
           Director
           Office of Science Coordination and Policy

Please find attached the meeting minutes and final report for the TSCA Science Advisory Committee on
Chemicals open public meeting held in Arlington, Virginia on December 3-4, 2019. This report addresses
a set of scientific issues being considered by the Environmental Protection Agency regarding the Peer
Review for the Draft Risk Evaluation for Methylene Chloride.

Attachment

1

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TSCA Science Advisory Committee on Chemicals Meeting Minutes and Final Report No. 2020-1

Peer Review for EPA Draft Risk Evaluation for Methylene Chloride

December 3-4, 2019

TSCA Science Advisory Committee on Chemicals Meeting,

Held at the Hyatt Regency Crystal City
2799 Richmond Highway (U.S. Route 1),
Arlington, Virginia 22202

NOTICE

The Toxic Substances Control Act (TSCA) Science Advisory Committee on Chemicals (SACC) is an advisory Committee operating in accordance with the Federal Advisory Committee Act and established under the provisions of TSCA as amended by the Frank R. Lautenberg Chemical Safety for the 21st Century Act of 2016. The TSCA SACC provides independent advice and recommendations to the U.S. Environmental Protection Agency (EPA or Agency) on the scientific basis for risk assessments, methodologies, and pollution prevention measures and approaches for chemicals regulated under TSCA. The SACC serves as a primary scientific peer review mechanism of the EPA, Office of Pollution Prevention and Toxics (OPPT), and is structured to provide balanced expert assessment of chemicals and chemical-related matters facing the Agency. Additional peer reviewers are considered and added on an *ad hoc* basis to assist in reviews conducted by the TSCA SACC. This document constitutes the meeting minutes and final report and is provided as part of the activities of the TSCA SACC.

The TSCA SACC carefully considered all information provided and presented by the Agency, as well as information presented by the public. The minutes represent the views and recommendations of the TSCA SACC and do not necessarily represent the views and policies of the Agency, nor of other agencies in the Executive Branch of the federal government. Mention of trade names or commercial products does not constitute an endorsement or recommendation for use.

The meeting minutes and final report do not create or confer legal rights or impose any legally binding requirements on the Agency or any party. The meeting minutes and final report of the December 3 - 4, 2019, TSCA SACC meeting represent the SACC's consideration and review of scientific issues associated with Peer Review for EPA Draft Risk Evaluation of Methylene Chloride. Steven Knott, MS, TSCA SACC Executive Secretary, reviewed the minutes and final report. Kenneth Portier, PhD, TSCA SACC Chair, and Todd Peterson, PhD, TSCA SACC Designated Federal Official, certified the minutes and final report. The report is publicly available on the SACC website (https://www.epa.gov/tsca-peer-review) under the heading of "Meetings" and in the public e-docket, Docket No. EPA-HQ-OPPT-2019-0437, accessible through the docket portal: https://www.regulations.gov. Further information about TSCA SACC reports and activities can be obtained from its website at: https://www.epa.gov/tsca-peer-review. Interested persons are invited to contact Todd Peterson, PhD, SACC Designated Federal Official, via e-mail at: peterson.todd@epa.gov.
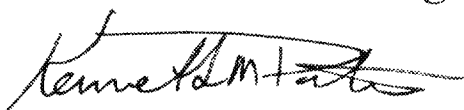
CONTENTS

TSCA Science Advisory Committee on Chemicals
Meeting Minutes and Final Report
No. 2020-01

Peer Review for EPA Draft Risk Evaluation for Methylene Chloride

December 3-4, 2019

TSCA Science Advisory Committee on Chemicals Meeting,

Held at the Hyatt Regency Crystal City
2799 Richmond Highway (U.S. Route 1),
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TSCA Science Advisory
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Date: 3/2/20

Todd Peterson, PhD
Designated Federal Official
TSCA Science Advisory
Committee on Chemicals
Date: 3/2/2020

Toxic Substance Control Act
Science Advisory Committee on Chemicals Meeting
December 3 - 4, 2019

Peer Review for EPA Draft Risk Evaluation of
Methylene Chloride

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LIST OF ACRONYMS AND ABBREVIATIONS

1-BP	1-Bromopropane
ACE	Acute-to-Chronic Estimation (Tool)
ADC	Average Daily Concentration
AEGL	Acute Exposure Guidance Level
AF	Assessment Factor
APF	Assigned Protection Factor
APHL	Association of Public Health Laboratories
BLS	Bureau of Labor Statistics
BMD	Benchmark Dose
BMDL	Benchmark Dose Level
BMDS	Benchmark Dose Modeling Software
CAA	Clean Air Act
CEM	Consumer Exposure Model
CNS	Central Nervous System
COC	Concentration of concern
COHb	Carboxyhemoglobin
COU	Condition of Use
DFq	Detection Frequency
DMR	Discharge Monitoring Report
DQE	Data Quality Evaluation
EC_{50}	Effect Concentration at which 50% of test organisms exhibit an effect
E-FAST	Exposure and Fate Assessment Screening Tool
EPA	Environmental Protection Agency
EPI Suite™	Estimation Programs Interface suite of models
EXAMS	Exposure Analysis Modeling System
FDA	Food and Drug Administration
GHS	Globally Harmonized System
GST	Glutathione S Transferase
HEC	Human Equivalent Concentration
HUC	Hydrologic Unit Code
HQ	Hazard Quotient
IUR	Inhalation Unit Risk
K_{oc}	Organic water-carbon partition coefficient
K_{oa}	Octanol-air partition coefficient
LADC	Lifetime Average Daily Concentration
LOAEC	Lowest Observed Adverse Effect Concentration
LOAEL	Lowest Observed Adverse Effects Level
LC_{01}	Lethal Concentration at 1%
LC_{50}	Lethal Concentration at 50%
LHS	Latin Hypercube Sampling
MCI	Molecular Connectivity Indices

MOA	Mechanism (Mode) of Action
MOE	Margin of Exposure
MSHA	Mine Safety and Health Administration
NAS	National Academy of Sciences
NCEA	National Center for Environmental Assessment
NESHAP	National Emission Standards for Hazardous Air Pollutants
NHANES	National Health and Nutrition Examination Survey
NIOSH	National Institute of Occupational Safety and Health
NOAEC	No Observed Adverse Effect Concentration
NOAEL	No Observed Adverse Effect Level
NOEC	No Observed Effect Concentration
NPDES	National Pollutant Discharge Elimination System
NRC	National Research Council
NTP	National Toxicology Program
OCSPP	Office of Chemical Safety and Pollution Prevention
OES	Occupational Exposure Scenario
ONU	Occupational Non-Users
OPPT	Office Pollution Prevention and Toxics
OSHA	Occupational Safety and Health Administration
OU	Occupational User
PBPK	Physiologically-Based Pharmacokinetic
PDM	Probabilistic Dilution Model
PEL	Permissible Exposure Limit
PF	Protection Factors
PESS	Potentially Exposed and Susceptible Subpopulations
POD	Point of Departure
POTW	Publicly Owned Treatment Works
PPE	Personal Protective Equipment
PRISM	Pesticide Registration Information System
QPPR	Quantitative Property-Property Relationships
QSPR	Quantitative Structure Property Relationships
RP	Respiratory Protection
RPD	Respiratory Protection Devices
RQ	Risk Quotients
SACC	Science Advisory Committee on Chemicals
SDS	Safety Data Sheets
SIC	Standard Industrial Classification
TK	Toxicokinetics
TSCA	Toxic Substances Control Act
TRI	Toxics Release Inventory
TWA	Time-Weighted Average
UF	Uncertainty Factor

USGS	United States Geological Survey
VOC	Volatile Organic Chemicals
VPP	Visual Peripheral Performance
WASP	Water Quality Analysis Simulation Program
WOE	Weight of Evidence

INTRODUCTION

The Toxic Substances Control Act (TSCA) of 1976, as amended by The Frank R. Lautenberg Chemical Safety for the 21st Century Act in 2016, Science Advisory Committee on Chemicals (SACC or Committee) completed its review of the set of scientific issues being considered by the Environmental Protection Agency (EPA) regarding the "Draft Risk Evaluation for Methylene Chloride." The Draft Risk Evaluation, supplemental files, and related documents in support of the SACC peer review meeting are posted in the public e-docket at https://regulations.gov (ID: EPA-HQ-OPPT-2019-0437). The initial notice of availability of the Draft Risk Evaluations, opening the docket for comments, and notice of meeting was published in the *Federal Register* on October 29, 2019 (84 FR 57866). The review was conducted in an open Committee meeting held in Arlington, Virginia, on December 3-4, 2019. Dr. Kenneth Portier chaired the meeting, and Dr. Todd Peterson served as the Designated Federal Official.

In preparing these meeting minutes and final report, the Committee carefully considered all information provided and presented by the Agency presenters, as well as information presented by public commenters. These meeting minutes and final report address the information provided and presented at the meeting, especially the Committee response to the Agency charge.

TSCA SACC Peer Review – Methylene Chloride

December 3 - 4, 2019:

Opening of Meeting – Todd Peterson, PhD, Designated Federal Official, EPA/Office of Science Coordination and Policy (OSCP)

Introduction and Identification of SACC Members – Kenneth Portier, PhD, Chair, TSCA Science Advisory Committee on Chemicals (SACC),

Introduction and Welcome – Mark Hartman, EPA/Office of Pollution Prevention and Toxics (OPPT), Immediate Office

Welcome and Introductory Comments - Alexandra Dapolito Dunn, Esq, Assistant Administrator, EPA/OCSPP

OPPT Technical Presentation – Overview of Methylene Chloride Risk Evaluation - Christopher Brinkerhoff, PhD, and Kara Koehrn, MS, EPA/OPPT/Risk Assessment Division (RAD)

Public Comments

Oral statements were presented as follows:

Bob Budinsky, Science Leader, Toxicology, Environmental Research and Consulting, The Dow Chemical Company

Melvin Andersen, PhD, Andersen ToxConsulting LLC

Richard A. Denison, PhD, Lead Senior Scientist, Environmental Defense Fund

Penelope Fenner-Crisp, PhD, DABT, Environmental Protection Network

Suzanne Hartigan, PhD, American Chemistry Council

Wendy Hartley, Private Citizen

Annie Hoang, Medical student, University of California, San Francisco

Jonathan Kalmuss-Katz, JD, Staff Attorney, Earthjustice Northeast Office

Lindsay McCormick, Program Manager, Chemicals and Health, Health Program, Environmental Defense Fund

Jennifer Sass, PhD, Natural Resources Defense Council

Robert Stockman, JD, Environmental Defense Fund

Bob Sussman, Safer Chemicals Healthy Families

Tracey Woodruff, PhD, Professor and Director, Program on Reproductive Health and the Environment, Department of Obstetrics/GYN, University of California, San Francisco

Written statements were provided to docket as follows:

Melvin Andersen, Andersen ToxConsulting LLC

Richard Denison, PhD, Lead Senior Scientist, Environmental Defense Fund

Environmental Defense Fund, Mass Comment Campaign

Tamara Fox, Vertex Pharmaceuticals, Inc

Suzanne Hartigan, PhD, Senior Director, Regulatory and Technical Affairs, American Chemistry Council

Sebastian Irby, Environmental Protection Network

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Kenneth A. Mundt, Senior Principal Health Scientist, Cardno ChemRisk

Laura Reinhard, Vice President and General Manager, Foam and Industrial Products, Honeywell

Bob Sussman, Safer Chemicals Healthy Families

EXECUTIVE SUMMARY OF SACC REVIEW

The Environmental Protection Agency (EPA or Agency) requested input and advice from the Science Advisory Committee on Chemicals (SACC or Committee) on issues posed as charge questions for the Methylene Chloride Draft Risk Evaluation (the Evaluation). The Committee discussed each charge question and developed recommendations.

On questions related to environmental fate and exposures of methylene chloride, the Committee commended the Agency for the extensive review contained in the Evaluation. Many environmental fate and exposure aspects of this Evaluation are far more complete than those developed for previously considered chemicals.

This Evaluation only considers Toxic Substances Control Act (TSCA) - related environmental fate and exposures issues, and hence only examines releases from point sources to water, exposures to workers/bystanders in workplaces, and exposures to methylene chloride during use of consumer products. All other releases and general population exposures to methylene chloride are covered under separate environmental legislation and hence risk from these releases are not discussed in the Evaluation. As a result, readers of this Evaluation receive a partial picture of risks, finding for example, that recycling and proper disposal present the only environmental hazards under TSCA. The Committee expressed concern that this incomplete picture of risks may be used to promote improper releases and disposal of methylene chloride, and the Committee encourages the Agency to rapidly finalize the assessment of all other releases and general population exposures to complete the risk picture for methylene chloride.

Several reviewers expressed concern that large quantities of methylene chloride are volatilized to ambient air from diverse and disperse uses and that there is no TSCA Condition of Use (COU) that provides a basis for setting any limit on these emissions. Several Committee members also suggested that the impact of methylene chloride emissions on ozone depletion as an endpoint should at least be mentioned in the Evaluation.

A short summary of methylene chloride's regulatory status under EPA, OSHA, and FDA would help readers understand the TSCA-focused conceptual model for methylene chloride and provide a more complete understanding of the limits of this risk evaluation.

Concern was expressed that many of the methylene chloride releases to the environment are unaccounted for, and the Committee recommended EPA consider using a mass-balance approach to match amount manufactured/imported with amounts used in products, recycled or disposed, and released to the environment. EPA may need to collect data to close data gaps that currently limit the ability to carry out such an analysis. Direct point source discharges to water are adequately discussed in this Evaluation despite a lack of surface water monitoring data for methylene chloride. Discharges to air, ground water, soils and sediments are not considered.

The Committee appreciated the larger number of test species for which exposure information is available and considered in this methylene chloride Evaluation. The Committee concurred that amphibians may be the most sensitive of aquatic vertebrate species. This points to a significant limitation of other draft risk evaluations where amphibian responses/testing are not typically available. The Committee would like to see EPA request these kinds of data for future TSCA evaluations.

A few improvements in data handling were recommended. A more thorough assessment of the gas chromatography method of measuring methylene chloride levels is needed to minimize the need for high uncertainty factors. Computation of a benchmark dose level (BMDL) or lethal concentration at one percent (LC_{01}) for each species is also recommended followed by choosing a toxicity value that is protective of 90% of species.

The Committee noted that the assessment would be improved if the Agency compared the locations of facilities releasing methylene chloride to the ranges of threatened or endangered species in river reaches.

The Committee disagreed on the characterization of environmental hazard as presented in the Evaluation. Justification is needed for assuming low potential hazard to terrestrial vertebrates from volatile methylene chloride. The Committee disagreed that the water flea (*Daphnia magna*) is a representative sediment dwelling organism and disagreed with how the no observed effect concentration (NOEC) for fish was determined. Barring changes to these values, the Committee recommended applying assessment factors of 100 to toxicity estimates.

The Committee extensively discussed issues related to occupation and consumer exposures and found the approaches and methods presented in the Evaluation to be logical and science-based but questioned some of the underlying assumptions. Assumptions were all discussed and recommendations for improvements provided related to the number of dermal exposures per day, time ranges and timing of exposures, as well as use and effectiveness of personal protective equipment (PPE). The Monte Carlo Simulation used to develop exposure statistics for occupational and consumer scenarios was poorly understood by some Committee members pointing to the need for further clarification.

The Committee was generally concerned over the use of limited data sets to extrapolate exposure among broader worker groups. The extent to which the available data, often collected by OSHA for specific regulatory purposes or in response to a variety of events, is generalizable to these broader groups even using the statistical models employed by EPA remains unclear. The Committee also recommended the Evaluation consider the impact of longer shift lengths and extended working years on acute and chronic exposure estimates. Specifically, typical exposure durations would be expected to be 8-hours in most scenarios, rather than 4-hours as proposed by EPA for many scenarios.

Dermal contact and inhalation exposures represent the most important routes of exposure in occupational settings. The assumptions made regarding these routes of exposure are scientifically sound and the Evaluation is a good effort to incorporate state of the science modeling with best available monitoring data. However, there was concern that the available limited data are being extrapolated to broader worker groups in ways that the original data were never intended to support. The data collected by OSHA are typically derived from targeted studies where a problem is suspected, although Adam Finkel, former standards director at OSHA, notes that typically the inspections are triggered by safety violations rather than chemical exposure violations (Finkel, 2017). This could imply that there is a potential for extrapolations to under- or overestimate general exposures in some cases. At the same time, the Committee thought that some of EPA's exposure concentrations and assumptions are likely to underestimate actual exposures, for example exposure durations are unrealistically short, workers are assumed to only be exposed to a single condition of use (COU), PPE use is assumed, and true variability in exposure concentrations is not well characterized. The extent of potential over or

underestimation needs further discussion.

The appropriate role of PPE in assessing occupational risks has been an issue before the Committee since its inception. In this Evaluation, responding to previous recommendations from the Committee, EPA provided exposure estimates under various assumed PPE use scenarios ranging from never-use to always-use of OSHA approved respirators and gloves for each condition of use. The Committee provided an additional recommendation for this Evaluation to improve how PPE is handled in assessing exposures to volatile chemicals such as methylene chloride. Most Committee members agreed that EPA's assumptions of PPE use likely do not reflect actual conditions in most workplaces.

To improve the estimates of acute exposures, the Committee recommended examining the impact of work-shift lengths beyond the assumed 4-hour and 8-hour shifts in the Evaluation. To improve the estimates for chronic exposure the Committee recommended extending the number of working years since recent data indicated the labor force participation rates continue to increase the fastest for the oldest segment of the population.

Properly estimating exposures for occupational non-users (ONUs) continued to be an issue of discussion for the Committee. The volatile nature of methylene chloride poses special concerns for ONUs and this Evaluation has made special efforts to better model their exposures under most COUs. Despite the lack of exposure data on ONUs, the Committee recommended further analysis including considering the distance from ONUs to occupational workers in assessing exposures and extending exposure duration to a minimum of 8-hours for central tendency.

The Committee identified no concerns with the approaches and models used to assess inhalation and dermal exposures to consumers of products containing methylene chloride. Peer-reviewed models are used in this assessment with default parameter settings linked to specific product use. Although consumer use is typically limited to occasional exposures, limited monitoring indicates the presence of methylene chloride at very low concentration in indoor air of residences and in ambient air. The Committee expressed concern that the general public is experiencing methylene chloride exposures beyond those identified from the TSCA-specific consumer use exposures.

The Committee agreed with the use of one double-blind controlled experiment examining central nervous system (CNS) effects related to methylene chloride exposures in humans to set the acute point of departure (POD) in the human health hazard assessment. Results seem to be supported by animal models. The Evaluation conclusions that CNS effects are concentration dependent with a steep dose-response requires additional strengthening by incorporating findings from other studies and incorporating the well-established toxicokinetics of methylene chloride. Issues with how these studies are handled in the quality review were discussed by the Committee which continued to push for improvements to this process. The Evaluation does not make full use of the available data on methylene chloride's acute human lethality. The Committee also discussed the potential immunotoxicity of methylene chloride and concluded that the Evaluation likely underestimates the risk and provided discussion to support this conclusion. Finally, the Committee felt that the Evaluation does not adequately address potential adverse myocardial effects of volatile organic compounds (VOCs) that are reported in the research literature.

The Committee found liver effects reasonable as the most sensitive non-cancer endpoint and supported by evidence, although it questioned parts of the approach and requested the Evaluation include more explanation. The selection of a lowest observed adverse effect concentration

(LOAEC)-to-no observed adverse effect concentration (NOAEC) uncertainty factor of three was considered not well justified and the Committee discussed the need for inclusion of a database uncertainty factor. The inhalation-to-dermal extrapolation also requires further clarification since it likely results in an overestimation of the dermal POD.

The Committee agreed with the Evaluation's review of several epidemiological studies of chronic exposures to methylene chloride and with the conclusion that evidence is inconclusive for methylene chloride-induced liver toxicity and cancer. Animal studies include a clear association with liver cancer, and there is also clear evidence for lung cancer via inhalation exposures. Mammary tumors are dismissed by EPA as uncertain without adequate justification. More discussion is needed to support the decision to estimate risk using liver and lung tumors when the calculation of the inhalation unit risk based on mammary tumors gives the highest unit risk.

The Committee was divided on whether available animal evidence supported a mutagenic mechanism of action (MOA) in which case linear low-dose extrapolation is appropriate or a non-genotoxic MOA in which case a non-linear threshold dose-response model is appropriate. Support for both is available in the research literature and the Committee was not able to agree on a best approach for the Evaluation. The Committee recommends that the EPA compute results under both assumed mechanisms and then provide justification for the final approach used.

This Evaluation makes extensive use of physiologically-based pharmacokinetic (PBPK) modeling to compute an internal dose for setting points of departure for risk calculation. The Committee generally agreed with the use of this model and approach. The Committee did request the Evaluation expand its discussion in the toxicokinetics section.

The inhalation unit risks developed by EPA for this methylene chloride risk evaluation are less protective than previous dose-response assessments by EPA and OSHA, all of which relied on the same underlying data. The Agency should explain why new inhalation unit risks were derived and exactly how they differ from previous assessments. The Committee discussed the role the glutathione S transferase, or GSTT1 genotype has in defining the response of an individual to methylene chloride exposures and recommended these individuals be considered a specifically susceptible subpopulation.

The Committee agreed that the Evaluation does a good job with risk characterization of methylene chloride, at least within the bounds set under TSCA. The Evaluation appropriately describes the assumptions underlying most of the derivation and calculations as well as providing the rationale for choosing to use some data over others, although many Committee members commented that assumptions and rationale should be more clearly presented. Sources of uncertainty are thoroughly discussed but not quantified, and vagueness remains in some places indicated by the Committee in its report. Several Committee members expressed concern that risks to ONUs could be underestimated. The Committee urged that the Evaluation replace the expression "no risk" with the expression "no unacceptable risk" in recognition of the inherent variability and estimator uncertainty associated with assessing even low-risk scenarios.

The Committee indicated that TSCA evaluations are improving in organization and clarity. Navigation was more difficult with this Evaluation, but this likely reflects the sheer size of the task and the resulting larger documentation. Improvements are still needed in completeness of the conceptual model and the Committee again recommended a mass-balance analysis be part of

this model. Concern was expressed that EPA does not have adequate methylene chloride production, use, and discharge data, and relies heavily on industry data and market reports. A Committee member suggested NIOSH or OSHA staff be added to the SACC since so many conditions of use are occupational.

**DETAILED COMMITTEE DISCUSSION AND RECOMMENDATIONS –
METHYLENE CHLORIDE**

As amended by the Frank R. Lautenberg Chemical Safety for the 21st Century Act on June 22, 2016, the Toxic Substances Control Act (TSCA), requires the U.S. Environmental Protection Agency (EPA or Agency) to conduct risk evaluation on existing chemicals. Methylene Chloride is one of the first ten chemical substances and the fifth of ten to undergo a peer review by the Science Advisory Committee on Chemicals (SACC). In response to this requirement, EPA has prepared and published a Draft Risk Evaluation for Methylene Chloride (the Evaluation). The Risk Evaluation process is the second step, following Prioritization and before Risk Management, in EPA's existing chemical process under TSCA. The purpose of risk evaluation is to determine whether a chemical substance presents an unreasonable risk to health or the environment, under the conditions of use, including an unreasonable risk to a relevant potentially exposed or susceptible subpopulation. As part of this process, EPA must evaluate both hazard and exposure, exclude consideration of costs or other non-risk factors, use scientific information and approaches in a manner that is consistent with the requirements in TSCA for the best available science, and ensure decisions are based on the weight-of-scientific-evidence.

The SACC was requested to provide advice and recommendations on the following questions.

Question 1: Environmental Fate and Exposure:

EPA qualitatively analyzed the sediment, land application, and biosolids pathways based on methylene chloride's physical-chemical and fate properties. Exposure estimates to the environment were developed for the conditions of use for exposures to aquatic organisms.

_Q 1.1_	**Please comment on EPA's qualitative analysis of pathways based on physical-chemical and fate properties.**

Response:

The Committee generally agreed that the pathway analysis presented in the Evaluation was reasonable and better presented than in the previous draft risk evaluations. The conceptual figure 2-1 (Evaluation, page 65) provided a nice overview of the pathways considered. However, adding values for environmental partition coefficients and relative rates of transport and transformation to the figure would provide a more quantitative description of the pathways.

Several Committee members questioned the exclusion of a terrestrial route of exposure to humans (e.g. vapor intrusion) and to terrestrial organisms (e.g. burrowing animals), suggesting that soil discharges were at least as likely as discharges via publicly owned treatment works (POTWs). Committee members were uncertain whether biosolid application was the only route of discharge to the soil environment that can be considered under TSCA. Other similar chlorinated solvents such as trichloroethylene and tetrachloroethylene are often found in groundwater and soil vapor. The Evaluation states on page 64 that "reports of detection in groundwater did not go through data evaluation and

extraction because groundwater pathways are outside the scope of this risk evaluation." It was unclear to what extent groundwater and soil contamination by methylene chloride will be evaluated by other agencies or under other environmental regulations. The Evaluation should clearly identify in the scope of the Evaluation those pathways specifically addressed by other regulations. This could be added to the conceptual model (Evaluation, Figure 2-1). If terrestrial discharges are considered, a model like EPA's Pesticide Registration Information System (PRISM) could be used to assess fate within the soil environment.

   o **Recommendation 1.1:** Better explain why no terrestrial pathways and receptors were considered and more clearly state what environmental pathways are addressed by other regulations.

The Evaluation indicated that methylene chloride in sediment is expected to be in the pore water rather than sorbed to the sediment organic matter, and that concentrations of methylene chloride are expected to be lower than concentrations in the water column. Several Committee members questioned the rationale presented in the Evaluation for not considering exposures to sediment dwelling organisms based on the organic water-carbon partition coefficient (log K_{oc} =1.4). Without a model that incorporates volatilization or sediment degradation rates, a log K_{oc} of 1.4 indicates that the sediment organic matter will have a concentration that is 25 times higher than the pore water concentrations.

Several Committee members indicated that piscivorous (fish-feeding) birds might also be impacted by methylene chloride volatilizing from surface waters near points of discharge and that this pathway should be analyzed for risk. Another Committee member suggested that a relatively long atmospheric half-life could result in a net flux of methylene chloride from the air into the water near large scale producers.

The Committee commented that there are more experimental physical-chemical property (Table 1.1) and fate (Table 2-1) data available for methylene chloride than for the previous chemicals evaluated. The experimental values obtained from the database contained within EPA's Estimation Programs Interface, or EPI Suite™[1] program and the estimated values derived from EPI Suite™ routines were considered to be high quality in the systematic review. Several Committee members expressed concern that these values lack information regarding variability or uncertainty—information that could impact the significance of some of the conceptual pathways. The Committee suggested expanding the discussion on data quality assessment and variability for the properties obtained from EPI Suite™ and other references. One Committee member observed that the procedures used for assessing acceptability in the quality review are much better defined for toxicology studies than for fate studies. It would be helpful if there was a better description of how the quality of the physical-chemical and fate properties are assessed. This need is illustrated by the finding that the hydrolysis value (half-life of 18 months) from Dilling et. al. (1975) was rated as 'low' while an estimated value (half-life of 4.3 x10^7 years) was ranked 'high' (Table 2-1). Paradoxically, the experimental value provided by Dilling et al. (1975) appears to be rated 'high' in the data quality evaluation (DQE) (supplemental file - 23 Draft Systematic Review Supplemental File Data Quality Evaluation of Physical-Chemical

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1 The EPI (Estimation Programs Interface) Suite™ is a Windows®-based suite of physical-chemical properties and environmental fate estimation programs developed by EPA and Syracuse Research Corp. (SRC).

Properties Studies Internal (Docket ID: EPA-HQ-OPPT-2019-0437-0025)). Experimental values of physical-chemical or fate properties are generally considered more reliable than estimated methods unless there are some obvious procedural or analytical problems. Another example of variability in a fate property mentioned by the Committee was the aerobic activated sludge biodegradation data listed in Table 2-1 (Evaluation page 63). The values from Lapertot and Pulgarin (2006) were considered high quality, even though these results were highly variable (0% in 28 days, 100% in 7 days). In this case, the Evaluation should provide a short discussion of why the values were dissimilar and present an estimated value(s) for comparison. Generally, physical-chemical properties can be considered high in quality if experimentally measured, medium in quality if derived from other experimental data or relationships (e.g., by algorithm), and low if determined by *in silico* models (e.g., quantitative structure property relationships (QSPR); Hansch et al. 1995).

The accuracy of an estimated property value varies depending on the estimation method used and how well the compound fits within the method's domain of applicability. When more than one estimation method is available within EPI Suite™, the rationale for selecting one estimation method over another should be provided. Instead of assigning high quality to all values estimated within EPI Suite™, the Committee suggested that it would be more appropriate to rank the values based on the reliability of the estimation method. For example, quantitative property-property relationships (QPPRs) are generally more reliable than QSPRs. For properties estimated using EPI Suite™, the Committee recommended specifically stating the estimation method that was used since several of the physical-chemical and fate properties can be estimated by more than one approach. For example, the organic carbon normalized sorption coefficient (K_{oc}) can be estimated from octanol-water partition coefficients or from structurally derived molecular connectivity indices (MCIs). In addition, several Committee members suggested estimating confidence intervals around each property and conducting a sensitivity analysis to determine whether potential variability would significantly change the outcome of the qualitative pathway analysis.

- o **Recommendation 1.2:** Incorporate a description of the uncertainty associated with the measured and estimated physical-chemical and fate properties into the draft risk assessment.

Several Committee members recommended that a mass balance approach be used to estimate methylene chloride discharges to the environment that aren't captured in the available databases such as the Toxics Release Inventory (TRI). Mass balance estimated discharges could be used along with environmental fate models like the Fugacity level 3 model in EPA's EPI Suite™ program to supplement limited monitoring data. For example, using the default emissions rates, the Fugacity level 3 model within EPI Suite™ predicts 11% of the mass released will be found in the soil.

- o **Recommendation 1.3:** Use a mass balance approach to provide a more realistic estimate of environmental discharges.
- o **Recommendation 1.4:** Use discharges estimated from the mass balance approach (recommendation 3) as input to a Fugacity level 3 or similar model to compare with (and supplement) any available environmental monitoring data.

Committee members recommended reviewing the Evaluation for incorrect environmental fate statements associated with implied rates to equilibrium of physical-chemical properties. This was previously discussed, and examples were provided in the Committee minutes on the review of the 1-Bromopropane (1-BP) draft risk evaluation document. For example, equilibrium properties such as Henry's law and vapor pressure do not inform volatilization rates in the environment. Please avoid statements like; "Due to its Henry's Law constant (0.00325 atm-m3/mole), methylene chloride is expected to volatilize rapidly from water" (Evaluation page 63, lines 832-833). That statement is incorrect since a Henry's law constant is an equilibrium value not a rate.

The term 'photolysis' refers to transformations mediated by light. This process can occur in surface waters, on surfaces and in the atmosphere by direct or indirect processes. The photolysis process referred to in Table 2-1 of the Evaluation should be clearly identified as 'atmospheric oxidation via the OH radical'.

The term 'sorption,' that includes both adsorption and absorption, is preferred over simply using 'adsorption' when discussing the interaction of an organic chemical with an environmental solid (see review by Doucette, 2003).

The Evaluation states that pore water concentrations of methylene chloride would be greater than sediment concentrations based on the low log K_{oc} value of 1.4. A log K_{oc} value of 1.4 indicates that equilibrium concentrations of methylene chloride would be 25 times higher in the organic matter of the sediment. The Committee suggests that the Evaluation text be more precise in how equilibrium properties are used to describe relative concentrations. For example, the Evaluation states (page 64): "Based on high volatilization, negligible adsorption, and possible biodegradation, concentrations of methylene chloride in land-applied biosolids are expected to be lower than concentrations in wastewater treatment plant effluents." This statement is true only if volatilization and/or biodegradation rates are rapid relative to sorption.

> o **Recommendation 1.5:** Be more precise in how equilibrium properties are used to describe relative concentrations.

The Committee recommended reporting Henry's law values as dimensionless air-water partition coefficients since partition coefficients directly relate chemical concentrations in the two phases that are in equilibrium. Also, the Committee suggested adding octanol-air partition coefficient (K_{oa}) values to the physical-chemical property table for all future chemicals. Values of K_{oa} can be estimated using EPA's EPI Suite™ program.

> o **Recommendation 1.6:** Add octanol-air partition coefficient (K_{oa}) values to the physical-chemical property table.

The Evaluation assumes that all sediment environments are anaerobic (see for example, Evaluation page 299). This is not likely to be true in many shallow, rapid flow rivers.

Evaluation page 64, states: "Based on its vapor density (2.93 relative to air), volatilized methylene chloride is expected to remain near ground level." This statement is incorrect. This would only be true for a very short period of time after release. At low concentrations and under most environmental conditions, methylene chloride would rapidly mix with air.

Q 1.2	**Please comment on the data, approaches and/or methods used to characterize exposure to aquatic receptors.**

Response:

Although likely conservative, the Committee generally agreed that it is not appropriate to use the Exposure and Fate Assessment Screening Tool (E-FAST) V2.0 model for predicting surface water concentrations for compounds like methylene chloride since this model does not address volatilization. The Agency's E-FAST V2.0 user documentation specifically recommends the model not be used if model assumptions are not met for the compound of interest. Modeled values generated from E-FAST were as high as 17,000 μg/L which is inconsistent with the highest measured concentration reported at 134 μg/L and most measured values around 5 μg/L or less. The use of an inappropriate environmental fate model reduces confidence in the overall approach used to conduct TSCA risk assessments. Several Committee members indicated that the E-FAST model should be modified to include volatilization, or the Evaluation should use a model more appropriate for methylene chloride, such as the EPA Water Quality Analysis Simulation Program (WASP) model or derivatives of this model (Ambrose, 1987). At a minimum, the half-lives predicted in the EPI Suite^{TM} program (1.1 h in rivers and in 89 h in lakes, based on volatilization from water) could be used to adjust the E-FAST predicted surface water concentrations.

- o **Recommendation 1.7:** The E-FAST model should be modified to include volatilization or a model more appropriate for methylene chloride, such as the EPA WASP model should be used instead.

There was concern that the much of the methylene chloride released to the environment is unaccounted for, as indicated by:

> "In 2015, 271 facilities reported a total of about 153.7 million pounds of methylene chloride waste managed. Of this total, about 96.9 million pounds were recycled, 15.6 million pounds were recovered for energy, 37.8 million pounds were treated, and 3.4 million pounds were released into the environment."

However, there is no explanation of what was meant by "treated" and one Committee member was concerned that this uncertainty implies that some of "treated" methylene chloride could eventually be released to the environment. Another Committee member indicated that the reported releases on page 79 seem too low, unless significant unassessed releases occur through the atmosphere. The Committee also reiterated the importance of clearly stating what environmental releases are covered by other regulations and are not associated with TSCA. This could address many of the questions/comments that Committee members had regarding non-aqueous discharges into the environment.

Several Committee members questioned why the quantitative environmental assessment is limited only to the measured water concentrations from the 2016 dataset and recommended that the discussion be expanded to better justify why all the available data was not used.

There is uncertainty in how the hydrologic unit code (HUC) flow data are used and many found the description of the numbers of facilities releasing to different HUCs to be confusing. Specifically, it is unclear whether the total flow value used an estimate for the basin or was this measured flow at the discharging facility. At least one Committee member indicated that geometric means should be used instead of arithmetic means as the appropriate descriptor.

The lack of aquatic system monitoring data for methylene chloride combined with the lack of a suitable fate model for volatile compounds results in limiting the ability to properly characterize aquatic organism exposure. The mass balance approach to approximating methylene chloride releases recommended in the Committee response to charge question 1.1, would provide better estimates of discharges into the environment than simply using the TRI which captures releases from only the larger users. One Committee member suggested the mass balance calculation be performed for each assessed facility, considering intake and documented disposal plus water and air releases. This can also estimate how much methylene chloride is unaccounted for in the current TSCA approach. In situations where no other objective information (e.g. measurement) is available, that difference should be assumed to enter the aquatic environment.

As discussed in charge question 1.1, the Evaluation did not consider sediment dwelling organisms. This was based on the relatively low estimated organic water-carbon partition coefficient (log K_{oc} =1.4). However, without a model that incorporates volatilization or sediment degradation rates, a log K_{oc} of 1.4 still indicates that the sediment organic matter will have a concentration that is 25 times higher than the pore water concentrations.

Finally, several Committee members indicated that piscivorous birds might be impacted by methylene chloride volatilizing from surface waters near points of discharge and that this oral pathway should be analyzed for risk.

- o **Recommendation 1.8:** The Evaluation should include discussion of the potential for piscivorous birds to be impacted by methylene chloride volatilizing from surface waters.

Question 2: Environmental Exposure and Releases:

EPA evaluated releases to water and aquatic exposures for conditions of use in industrial and commercial settings. EPA used Toxics Release Inventory (TRI) and Discharge Monitoring Report (DMR) data to provide a basis for estimating releases. EPA used these releases and associated inputs within EFAST 2014 to estimate instream chemical concentrations and days of exceedance. EPA also evaluated monitored values of methylene chloride in surface water and where possible compared those values to estimated release concentrations.

Q2.1	Please comment on the approaches, models, and data used in the water release assessment including comparison to monitored data.

Response:

Many of the Committee's concerns associated with this charge question were addressed previously in charge questions 1.1 and 1.2. The Committee considered comparisons between E-FAST-generated surface water concentrations and monitoring data as inappropriate since the model is not applicable for volatile compounds like methylene chloride. Even if the model was applicable to methylene chloride, the number of samples collected was too small to draw definitive conclusions on possible associations between measured concentrations in surface water and predicted concentrations from facility releases.

As mentioned in charge question 1.2, the lack of surface water monitoring data for methylene chloride was a concern to Committee members, as was the insufficiency of just looking at TRI and DMR data for releases. Given that only facilities of a certain size are required to submit to these reports, it is likely that overall release data are underestimated. To address this issue, Committee members were generally in favor of using a mass balance approach to provide more realistic estimates for environmental releases. It was also suggested that releases from multiple facilities located in the same hydrologic unit be combined and addressed using a more appropriate environmental fate model. To address the lack of monitoring data, several Committee members recommended that the EPA begin exploring other potential monitoring data sources such as the Association of Public Health Laboratories (APHL). While the APHL represents public health laboratories that focus primarily on infectious agents, they do have an environmental health biomarkers project and many of the labs support their state's environmental enforcement/conservation programs. Another suggested database that could be used to estimate releases to surface waters was the National Emission Standards for Hazardous Air Pollutants (NESHAP). This database contains purchase, disposal, and air release records and any differences could be assumed as water releases.

Another concern raised by several Committee members was the uncertainty associated with many of the model inputs and assumptions. For example, assuming methylene chloride releases are fixed and constant for each facility does not take into account the uncertainty in the estimated or assumed number of days per year of release. A sensitivity analysis should be conducted to evaluate the importance of model input uncertainty.

Recommendations:

- o **Recommendation 2.1:** Modify E-FAST to include volatilization or use more appropriate model.

- o **Recommendation 2.2:** Use mass balance approach to better predict releases into the environment.

- o **Recommendation 2.3:** Consider exploring other potential monitoring data sources such as the APHL or the NESHAP.

- o **Recommendation 2.4:** Better document the uncertainty of model inputs and assumptions and categorize the impact of this uncertainty on exposure estimates.

Q 2.2	**Please provide any specific suggestions or recommendations for alternative data or estimation methods, including modeling approaches, that could be considered by the Agency for conducting or refining the water release assessment and relation to monitored data.**

Response:

As mentioned in charge questions 1.1, 1.2 and 2.1, the Committee recommended modifying E-FAST to include volatilization or using other more appropriate environmental models like EPA's WASP (Ambrose, 1987) or Exposure Analysis Modeling System (EXAMS) that incorporate volatilization. This would enable a more realistic comparison between measured and modeled surface water concentration and address concerns of the Committee associated with the methylene chloride monitoring data being obtained far away from the discharging facility. A more detailed description or justification of model selection should be presented. (see Recommendation 1.7).

Since relatively little measured surface water concentration data are available for methylene chloride, one Committee member suggested using monitoring data from other similar but data rich chlorinated volatile solvents to evaluate models and model predictions. Another Committee member suggested that using the NESHAP might be another approach to estimate releases to water since it contains purchase records, disposal records and air releases. The remainder could be interpreted as releases to water.

- o **Recommendation 2.5:** Use available surface data from similar chlorinated solvents to evaluate models.

- o **Recommendation 2.6:** Consider using additional databases, such as the NESHAP, that might better facilitate prediction of releases into the aquatic environment.

Related to concerns expressed in charge question 2.1, the Committee suggested that a sensitivity or uncertainty analysis be conducted with any modeling efforts. For example, the removal from wastewater treatment was estimated to be 57% and this value was used in the model with no variation or uncertainty considered.

- o **Recommendation 2.7:** Perform limited sensitivity/uncertainty analysis on model inputs and incorporate findings into the Evaluation.

- o **Recommendation 2.8:** Modify E-FAST to include volatilization or use more appropriate models such as WASP or EXAMS.

Question 3: Environmental Hazard:

EPA evaluated environmental hazards for aquatic species from acute and chronic exposure scenarios.

Q 3.1	**Please comment on EPA's approach for characterizing environmental hazard for each risk scenario (e.g. acute aquatic, chronic aquatic). What other additional information, if any, should be considered?**

Response:

The Committee disagreed on the characterization of environmental hazard as presented in the Evaluation. The Committee disagreed on whether the proposed hazard values (or ranges) based on geometric means from various acute and subchronic/chronic studies were properly estimated. The Committee concurred that amphibians are likely among the most sensitive aquatic species (Evaluation pages 29 and 285). This conclusion suggests that obtaining toxicity data on amphibians and/or accounting for amphibian sensitivity should be a part of all TSCA risk evaluations. Manufacturers and users of chemicals considered for regulation under TSCA should be required to provide data on amphibian toxicity.

Exposure to terrestrial vertebrates (e.g., wildlife for example via drinking) was considered unimportant or irrelevant (Evaluation, page 285) in the Evaluation. However, the logic for exclusion and/or justification for low expected potential hazard are not presented in the Evaluation. The Committee recommended adding justification to the Evaluation by quoting data, offering logical arguments, or presenting model results to support a conclusion of insignificant exposures to wildlife.

- o **Recommendation 3.1:** Add an assessment of potential exposures to terrestrial vertebrates through inhalation and soil contact.

The Committee was pleased to see three fish studies used to evaluate toxicity but considered the LC_{50} endpoint not protective of environmental receptors. An LC_{50} (or LC_{10}) is fundamentally a point on a dose-response curve. Dose response curves differ from species-to-species hence small changes in dose may be more impactful for one species than another. As such, it is incorrect to use the geometric mean of LC_{50} values from multiple species as the measure of lethality (the integration method mentioned in Evaluation, page 203). The Committee suggests calculating LC_{01} values for all species and using the lowest value as the POD. The Committee considers the LC_{01} of 9.7 µg/L for the common European frog (*Rana temporaria*) to be more easily justifiable than the LC_{50} for Northern salamander *(Ambystoma gracile)* of 23.03 mg/L. Thus, if the Agency chooses not to proceed with the approach described above and insists on using a (single or

integrated) LC_{50} as the endpoint for hazard assessment, the 23.03 mg/L LC_{50} for *A. gracile* would be more appropriate than the value proposed in the Agency's current Evaluation, because this lowest measured LC_{50} represents 17% of amphibian species in a species sensitivity distribution.

- o **Recommendation 3.2a:** Develop LC_{01} values for test species and select the lowest value for use in hazard quotient (HQ) determination.

- o **Recommendation 3.2b:** If Recommendation 3.2a is not considered a viable approach, then apply an assessment factor of 100 (see Keinzler et al. 2017) to the daphnia toxicity estimate proposed in the current Evaluation.

The Committee noted that a nine-day exposure (Evaluation, page 212) is not a chronic exposure for salamander. Typically, chronic exposures represent >10% of an organisms' life span. Ambystomid salamanders can live >25 years in captivity, therefore, a chronic exposure would be at least > 2.5 yrs. Since mortality was assessed (or inferred based on significant terata) a nine-day exposure is simply repeated dose or borderline subchronic exposure at best. This does not represent a chronic exposure. However, the value used with the assessment factor (AF) of 10 seems to be consistent with the conclusions of the authors regarding significant adverse reproductive impairment. Applying an additional AF of 10 produces a value of 0.09 mg/L that is consistent with the comments of Black et al. (1982). Calculating an acute-to-chronic estimate using the Acute-to-Chronic (ACE) tool could provide corroborative evidence in support of this value. Additionally, a BMDL lower bound could be estimated using Black et al. (1982) data.

Water flea (*Daphnia magna*) and grass shrimp (*Palaemonetes pugio*) were used as representative species for assessing acute toxicity. The Committee agreed with the effect concentration at which 50% of organisms exhibit an effect (EC_{50}) and NOEC estimates presented in the Evaluation. Daphnia was used as a surrogate species for estimating hazard in sediment invertebrates (Evaluation, page 205). Since daphnia feed through the entire water column and in sediment, it is improper to consider daphnia as representative of sediment dwelling organisms. If daphnia *must* be used, then the AF or uncertainty factor (UF) should be higher, as noted by Keinzler et al. (2017). Further evaluation of aquatic invertebrate data reveals that the geometric mean for aquatic invertebrates (i.e., 179.98 mg/L; Evaluation page 207) or the underlying values for aquatic invertebrate toxicity (page 204) seem to be in error. The values from the cited studies in the problem formulation are 27,109, 220, 256, 412, 1250, and 1682 mg/L. The geometric mean of these values is not 180 mg/L. The species and LC_{50} values for each study used should be listed along with an indication of whether measured or nominal data were used. Also please note many of these LC_{50} values are from studies that do not report any measured or nominal concentrations for exposures.

The Committee did not agree with the selection of 5.55 mg/L as the NOEC for teratic larvae in the rainbow trout study (Evaluation, page 207) since teratogenic effects were observed at this value. Black et al. (1982) corrected survival numbers for control survivals (Evaluation, page 205 and Table MC3-1 presented below). Therefore, the 85% survival was relative to control survival. Thus, there is no rationale for excluding low concentration effects. A NOEC cannot reasonably be defined as a concentration, 0.41 mg/L, in which 15% mortality occurred. There was a lower concentration of 0.042 mg/L which demonstrated a 93% survival (Table MC3-1). The value of 0.041 mg/L would be more appropriate to use in this case. This directly influences the outcome of risk assessments, as HQs would be increased by a factor of 10 for fish if 0.051 mg/L was used.

Furthermore, immobile fish (page 203) in this study could be considered mortalities in current testing protocols. This nuance is protocol dependent. For the sake of conservatism, the Agency should justify not considering immobile fish as mortalities.

Table MC3-1. Toxic Responses of Rainbow Trout During Exposure to Methylene Chloride. Percent hatchability shown in parentheses represents number of organisms displaying teratogenic effects. (Data from Table 9, page 44 of Black et al. 1982, reproduced with permission granted by Dr. L. Ormsbee, Director, Water Resources Research Institute, University of Kentucky)

Test Species	Toxicant Concentration (mg/L)	Percent Hatchability	Percent Survival Normal Organisms	
			Hatching	4 Days Post hatching
Rainbow Trout	0.008 ± 0.001	100(0)	100	100
	$0.042 \pm " 0.004$	93(0)	93	92
	0.41 ± 0.04	86 (0)	86	85
	5.55 ± 1.06	73 (2)	72	70
	23.1 ± 1.7	48(9)	44	44
	36.5 ± 2.8	18(49)	9	9

Black et al. (1982) noted in their acute study: "... that developmental stages of certain amphibian species may be affected by concentrations at approximately 100 μg/L and that concentrations at or above 1 mg/L may produce substantial reproductive impairment." This suggests that the proposed effect concentration in the Evaluation of 0.9 mg/L is approximately 10-fold higher than what Black et al. suggests could be harmful.

The United States Geological Survey (USGS) publication (Zogorski et al. 2006) "VOCs in the Nation's Ground Water & Drinking Water Supply Wells" contains maps of VOCs distributions in the nation; methylene chloride is included. The Agency should consider inclusion of those maps of methylene chloride distributions in streams in the report. Similarly, E-FAST can provide overlays of endangered species for river reaches modeled in the valuation. The Agency should use E-FAST routines that map overlap of methylene chloride distributions in the streams with threatened and endangered species ranges, including amphibians [i.e. Hellbender (*Cryptobranchus alleganiensis*)].

   o **Recommendation 3.3:** Present an analysis of how home ranges of threatened and endangered species overlap with known source areas impacted by methylene chloride releases.

General comments:

The EC$_{50}$ values of 242.41 and 135.81 mg/L (Evaluation, page 203) cannot be known to this level of precision.

The Evaluation citation "Wilson, JEH. (1988)" is incomplete. It does not contain the name of the journal or the book. Even though the purity of the test substance was not specified in the paper, the Committee questioned whether the purity could be assigned or assumed using the average purity of methylene chloride on the market.

The summary of environmental hazard in Section 3.1.5 needs one or two concluding sentences that compare effects of methylene chloride across different trophic levels.

Question 4. Occupational and Consumer Exposure:

EPA evaluated acute and chronic exposures to workers for conditions of use in industrial and commercial settings. For exposure via the inhalation pathway, EPA quantified occupational exposures for both workers and occupational non-users based on a combination of monitoring data and modeled exposure concentrations. For exposure via the dermal route, EPA modeled exposure for workers, accounting for the effect of volatilization. EPA assumed dermal contact with liquids would not occur for occupational non-users. EPA assumed that workers and occupational non-users would be adults of both sexes (>16 and older, including women of reproductive age).

Q 4.1	Please comment on the approaches and estimation methods, models, and data used in the occupational exposure assessment.

Response:

In general, the Committee finds that EPA has done a good job in explaining the rationale and assumptions used to derive estimates of inhalation and dermal exposures for occupational users (OUs) and occupational non-users (ONUs). The Evaluation for methylene chloride is an improvement over prior evaluations reviewed by the Committee, partly reflecting EPA's responsiveness to the prior reviews about improving clarity and transparency. As was the case with these prior evaluations, there were limited exposure measurement data available for OUs and, most deficiently, for ONU's. To compensate for this limitation, EPA relies more on the use of exposure models as compared to measurements, which the Committee had recommended in the prior review of the 1,4 Dioxane Evaluation.

Clearly, models are the alternative when no measurement data are available, for either OUs or ONUs, assuming reasonable conditions of use based on professional judgment and users input. In particular, EPA could explore modeling options for estimating ONU's exposures, since there are no measurements. Assigning the OUs central tendency exposure may not necessarily be sufficiently conservative, depending on the specific use scenario and the location of the ONU with respect to the user(s). The Agency should consider exploring different categories of ONUs (e.g., workers who do not handle methylene chloride directly, but whose job requires them to be in the same area as users; cleaning staff that can be exposed after hours to residues present in the work area, or office/managerial workers that could be incidentally exposed when visiting a work area but are not at risk from exposure routinely) because their potential exposure risk likely varies.

Some of the measurement data available to EPA was not used because critical sample collection information is not reported by the source of the data. Sometimes, the missing information is as cursory as the duration of sample collection, which is routinely recorded as part of area or personal monitoring but, for whatever reason, may not have been reported to EPA. It is not clear whether EPA exhausted all reasonable means to obtain the missing information, for example by

contacting the authors of a publication or company report, or the laboratory that analyze the sample. It was not clear that EPA has a process in place to obtain critical missing information on uses, PPE, or area and personal monitoring data. The process should take place early in the risk evaluation process to allow sufficient time for relevant stakeholders to provide the missing information to fill data gaps and/or strengthen the available information already present.

- o **Recommendation 4.1** – The Committee recommended EPA develop a process to identify critical missing information on uses, PPE, or area and personal monitoring data.

The Evaluation groups methylene chloride area and exposure measurement data pre- and post-revision of the permissible exposure limit (PEL) from 500 ppm to 25 ppm in 1997, which could lead to overestimation of exposure. This is a conservative approach and therefore, more worker protective. The Analysis of these OSHA inspection data suggests that exposure levels did not change dramatically before and after 1997, so that the data could be combined for the purpose of exposure estimation. The argument for combining the two periods could be strengthened by an expanded discussion of the mix of products, processes, and/or worker practices before and after 1997, about which EPA claims to not have received information. Again, it is not clear whether EPA contacted users proactively to obtain this information. However, it is likely that producers and users of methylene chloride started implementing changes before 1997, in advance of the expected promulgation of the 25 ppm PEL. This could also contribute to explain the relatively limited reduction in exposures between the two periods.

The Agency should be highly commended for a significant improvement in the presentation and discussion of PPE compared to prior Evaluations. The Evaluation for methylene chloride describes OSHA's requirements, limitations of PPE (respirator and glove protection), and the lack of specific information on users' practices regarding PPE. The Evaluation repeatedly reminds the reader about the uncertainties on appropriate PPE use and, as a result, there is a more balanced presentation of exposures and risk estimates with and without PPE. Nonetheless, emphasis on the insufficient information on appropriate PPE use should be strengthened. It is not clear how lack of knowledge about appropriate use of PPE, or of components in products containing methylene chloride (which could synergistically or additively reduce PPE effectiveness) is reflected in the level of confidence on exposures without PPE as compared to PPE use. EPA should be more transparent in this regard. EPA should increase efforts at obtaining specific information on PPE use from users in future Evaluations. The universe of PPE manufacturers and distributors is limited, and it does not appear that they are aware of their clients' uses and needs. The Agency could reach out to producers and distributors of PPE to determine if they could provide useful information.

Another consideration in describing sources of uncertainty more transparently is the potential for introducing bias when classifying uses and type of worker activities into these categories. If the exposure estimate is based on reported measurement data, and that data is for one or very few worker activities within the user/occupational exposure scenario (OES) category, it could potentially underestimate or overestimate exposures for other worker activities included in the same OES. The Agency should provide a more detailed description of this potential bias. In addition, while EPA describes the sources of uncertainty in exposure estimates (including those related to PPE), it is not clear how these uncertainties translate into data quality and overall

confidence designations.

The Committee was concerned with the assumption of only a single dermal exposure per day and thought that this assumption results in an underestimation of potential exposures. Also, it is unclear why the 15-minute and 30-minute samples (Evaluation, Section 2.4.1.2.1, page 115, Table 2-29) are categorized using the bounds of 15 to 29 minutes and 30 to 59 minutes, respectively, given that, for instance, a 29-minute exposure is closer to a 30-minute sample than a 15-minute sample.

- o **Recommendation 4.2** – Provide a more thorough explanation of why the assumption of a single dermal exposure per day was used.
- o **Recommendation 4.3** – Either better justify the time ranges used or adjust ranges of 15 to 22.5 minutes and 22.5 to 45 minutes for the 15-minute and 30-minute samples, respectively.

- o It is unclear from the text of the report why the near-field indoor air speed is not related to the air exchange rate and the volume of the room. It is also unclear why the speed of air movement in the near-field would not be the same as for the rest of the room unless some type of additional ventilation (i.e., a fan) was used in the near-field. The use of additional ventilation was not mentioned in the text. Also unclear is why movement of chemical in the air was modeled using air speed rather than diffusion between the near-field and far-field.

- o **Recommendation 4.4** – Clarify the issues related to near-field air wind speed and use of additional ventilation in the scenario.

The Committee suggested the need for more clarity and justification for the assumptions made in the Monte Carlo analysis used in the occupational exposure assessment.

The Committee was unsure why the number of spray applications per brake job was set to a constant in the Monte Carlo analysis rather than as a variable with associated distribution. The comment in Table_Apx F-1 of the Evaluation, for number of applications per job (N_A) is uninformative.

The Committee acknowledged the usefulness of the uniform distributions (Distribution Type = Discrete in Table_Apx F-1) in a Monte Carlo analysis, but its application for a particular input parameter in the Monte Carlo simulation needs to be justified just as any other distributional type must be justified.

- o **Recommendation 4.5** Expand the discussion on the selection of distributions for the Monte Carlo analysis, particularly for specification of the uniform distributions as the most appropriate choice for an input parameter.

- o **Recommendation 4.6**: Expand the description and rationale for setting an input parameter to a constant or investigate whether a distribution provides a better description of the exposure range.

The Committee was unable to duplicate estimates for average daily concentrations (ADCs) and lifetime average daily concentrations (LADCs) presented in Tables 2-39, 2-41 and 2-45 (Evaluation, pages 122, 124 and 128) using the approach and equations of Section 2.4.1.1

(Evaluation, page 107) and the available 8-hour Time-Weighted Average (TWA) exposure concentrations. These estimates differ enough that they do not appear to be due to rounding in the calculations. These tables were the only instances where the exposure estimates are from modeling the data rather than calculated directly from monitoring data. If the estimates derived from modeling were handled differently from direct estimates the text should discuss this.

- o **Recommendation 4.7**: Ensure ADC and LADC estimates are correct and explain discrepancies between estimates derived using Eq. 2.5 and estimates derived from the 8-hour TWA measurements.

It was unclear why preference was not given to limit use of monitoring data to that collected after the PEL was established. There were no explicit issues with earlier data being used in the absence of data collected after the PEL. The statement that "…incremental general exposure reductions due to the PEL change…" indicate that "…exposure data from before the PEL are adequate" (Evaluation, Section 2.4.1.1, page 108, lines 1852-1854) needs to be expanded. The Committee noted that data collected after the PEL should simply be given more weight. Additionally, it was unclear exactly what EPA meant by "…sites used to collect occupational exposure monitoring data for workers were not selected randomly" (Evaluation lines: 1850-1851) and appears to be indicating that bias was included in monitoring data.

- o **Recommendation 4.8**: Provide more context and added justification for how the OSHA monitoring data collected post-1997 are used, describe clearly biases in the OSHA data and any associated uncertainties in the exposure estimates.

The value for Y_{derm} in Table 2-33 of the Evaluation is used for the calculations, the calculated numbers don't match those in the Table 2-57, page 138. It appears that this is because the value for Y_{derm} should be 0.9 instead of 1.0 here. The summary table for dermal exposure estimates (Table 2-85, page 165) shows a value of 0.9 for this worker category.

- o **Recommendation 4.9**: Reconcile this discrepancy and adjust the text accordingly.

There is a discrepancy between the Yderm value reported in Table 2-57 (i.e., 1.0, Evaluation page 138) and the corresponding value in Table 2-85 (i.e., 0.9, Evaluation, page 165). EPA should verify the dermal dose calculations for the Commercial, Adhesive and Caulk Removers, and Spot Cleaning scenarios were performed with Y_{derm}=0.9.

The text (Section 2.4.1.2.19, page 156, lines 3138-3145) is not clear on how the minimum, maximum and mean values from the Ukai et al. (1998) study are used to estimate the TWA used for calculating the ADC and LADC.

- o **Recommendation 4.10**: Clarify how the minimum, maximum and mean values from the Ukai et al. (1998) study are used to estimate the TWA for calculating the ADC and LADC (Section 2.4.1.2.19, page 156, lines 3138-3145).

The rationale for setting the modeling inputs for the weight fraction (Evaluation, Section 2.4.2.3, page 168, lines 3449-3452) is unclear. Why is the maximum and minimum of the weight fraction used if the value is less than 40% but the maximum, minimum and midpoint are used if the weight fraction is more than 40%.?

- o **Recommendation 4.11**: Explain why only the maximum and minimum were used to determine modeling inputs if the weight fraction was less than 40% but the maximum,

minimum and midpoint were used if the weight fraction was more than 40% (Section 2.4.2.3, page 168, lines 3449-3452).

- o **Recommendation 4.12**: The mean and standard deviation should be included in the parameter distribution tables for the specific lognormal distributions used. Parameters used to define the other distributions are included.

Table Appendix F.1 of "Supplemental Information on Releases and Occupational Exposure Assessment" (page 270) shows that a discrete distribution was used for Weight Fraction. However, the actual text reads as if the Weight Fraction was determined by sampling from two separate distributions with the sampling from the second dependent on the sampling from the first distribution. Additionally, Table Appendix F.1 in Appendix F of "Supplemental Information on Releases and Occupational Exposure Assessment" (page 270) does not show a distribution for N_J (number of brake jobs per work shift). No justification is provided as to why this was not considered a variable with an appropriate discrete distribution assumed.

- o **Recommendation 4.13**: Table_Apx F of "Supplemental Information on Releases and Occupational Exposure Assessment" should be updated to more clearly represent what was actually done.

Table Appendix F-3 of "Supplemental Information on Releases and Occupational Exposure Assessment" (page 280) shows a lower bound for the vapor generation rate of 0.015, but the text describing this parameter (page 285) gives a value of 0.02.

- o **Recommendation 4.14**: Table Appendix F-3 of "Supplemental Information on Releases and Occupational Exposure Assessment" and/or associated text should be updated to represent the correct value. EPA should revise the Evaluation and Supplemental documents to verify that values for parameters in Tables and the text are all reported to the same precision as used in calculations and models.

Much of the human exposure assessment in this Evaluation relies on monitoring data collected before OSHA lowered the PEL in 1997. The rationale for this appears to be based on comments from Finkel (2017) that reviewed data from OSHA prior to and after the PEL changes and concluded that lowering the PEL had little impact to a general average of measured methylene chloride exposures in the OSHA database. It was not at all clear that the data supports a general conclusion that all the data remains relevant.

- o **Recommendation 4.15**: Analyze the OSHA data using appropriate statistical methods for each use category and cite the results to justify that the old monitoring data remains relevant for assessing exposures in 2019.

The Committee was generally concerned over the use of limited data sets to extrapolate exposure among broader worker groups. While the EPA has established a mathematical approach to identify the central tendency and high-end values when the distribution is unknown, the current data quality assessment does not take into account whether the data are generalizable to the exposures among the entire set of workers which the data is being used to represent. The data collected by OSHA typically targets locations where a concern has been identified, although Adam Finkel (2019) explained that inspections typically were prompted by safety violations rather than PEL violations. The Evaluation does not provide sufficient information on the reasons used by OSHA to collect data at targeted sites, and therefore the potential for overestimation or bias of general exposures for a specific use is not easily determined.

- o **Recommendation 4.16**: Include in the Evaluation report or in supplemental documents, additional information on the basis and purpose of data collection to provide better understanding about why the data reported by OSHA were collected.

For use categories where EPA analysis determined that the exposure is above the PEL, the Committee suggested that an additional analysis could be conducted based on the approach of setting the maximum exposure based on data for those companies that are following either OSHA and/or EPA NESHAP regulations.

- o **Recommendation 4.17**: Evaluate the representativeness of data sets or express the uncertainty in the extrapolated exposures.

The hierarchy used for exposure assessment is narrow in its scope. Specifically, data from OSHA as provided by Finkel should be incorporated into each of the exposure scenarios using the Standard Industrial Classification (SIC) codes in the database to guide determination of appropriate work groups.

- o **Recommendation 4.18**: Incorporate multiple exposure sources and possibly modeling whenever possible.

The Agency's reliance on appropriate use of personal protective equipment (PPE), including both respirators and gloves, is not supported by current research literature or industrial hygiene practice.

The mere presence of a regulation requiring respirators does not mean that they are used or used effectively. Inadequacies in respirator programs are documented. Respirators require multiple respiratory protection (RP) compliance factors in order to perform as certified. Brent et al. (2005) used data from the NIOSH and Bureau of Labor Statistics (BLS) joint survey on Respirator Usage in Private Sector Firms, (BLS, 2001) to examine the adequacy of respirator protection programs in private industries. They found "large percentages of establishments requiring respirator use [under OSHA or the Mine Safety and Health Administration (MSHA) regulations] had indicators of potentially inadequate respirator programs." Later, Janssen et al. (2014) reported that "APFs do not apply to RPD used in the absence of a fully compliant RP program; less than the expected level of protection is anticipated in these situations."

Moving beyond program elements, the frequency of *proper* use of gloves and respirators is largely unknown. The Committee suggested that the NIOSH BLS respirator usage survey can be used to provide industry-based estimates of respirator program effectiveness, which could then be employed to set the best Assigned Protection Factor (APF) for an industry. One Committee member indicated that the high-end exposure scenarios do not include protection factors derived from assumed respirator use.

On page 110, lines 1918-1922, the Evaluation states:

> "Regarding glove use, data about the frequency of effective glove use – that is, the proper use of effective gloves – is very limited in industrial settings. Initial literature review suggests that there is unlikely to be sufficient data to justify a specific probability distribution for effective glove use for a chemical or industry."

The EPA should present and/or reference the literature reviewed and should be clear when they believe that PPE will be used within an industry and present the appropriate justification. The

EPA should indicate when/if the assessment of PPE use was made based on professional judgment.

On page 111, beginning on line 1934, the Evaluation states:

> "The European Centre For Ecotoxicology and Toxicology of Chemicals Targeted Risk Assessment (ECETOC TRA) model represents the protection factor of gloves as a fixed, assigned protection factor equal to 5, 10, or 20 (Marquart et al., 2017), where, similar to the APR for respiratory protection, the inverse of the protection factor is the fraction of the chemical that penetrates the glove."

These default protection factors (PFs) are theoretical in nature, not tested in actual use. The Evaluation does acknowledge (also on page 111, line 1942) the limitations in using the assigned PF of 20. One Committee member cautioned against the use of PFs of 10 or 5, especially in the high exposure use scenarios. In the description of the conceptual model, Cherrie (2004) indicated that:

> "The dependence of glove protection factor on the duration of the task is very different from respirators where it is assumed that the protection factor is constant and independent of the concentration of contaminant challenging the device."

Cherrie (2004) demonstrates that for long duration task (beyond 360 minutes) scenarios, the PF of gloves continues to drop below 10. For this reason, in the high-end exposure scenario where workers are expected to be exposed for longer duration at higher chemical concentrations, the glove PF should be limited to a PF of five or one.

- o **Recommendations 4.19:** For high-end exposure scenarios, limit the glove PF to five or one, regardless of industry.

Exposure modeling in the Evaluation assumes dermal exposure limited to one event/day – even in the high-end exposure scenario. This is likely a gross underestimate of exposures, and, as acknowledged in the Evaluation, workers are likely to experience repeated contact with chemicals throughout the day.

- o **Recommendations 4.20:** When modeling dermal exposure, EPA should consider the possibility of more than one exposure per day per worker since workers are likely to encounter the chemical throughout their workday. Multiple exposure events are even more likely in high-end exposure scenarios.

The Committee noted that non-occlusive clothing is non-protective and could encourage dermal-to-vapor uptake.

The Committee was concerned about how the Evaluation characterizes occupational inhalation exposure of methylene chloride as used in manufacturing (domestic manufacture), processing (as a reactant) distribution, industrial and commercial use as a laboratory chemical for all other chemical product and preparation manufacturing.

Approaches and estimation methods for characterizing inhalation exposures presented in the Evaluation seem reasonable and well-explained. The assumption that volatilization is accounted for in the estimates of dermal exposure to occupational users needs further

clarification/justification since some text (see for example the discussion in the Evaluation, pages 110-111 and 165) seem to imply otherwise.

The estimate of 1,070 sq cm (two full hands) is appropriate for a surface area estimate. The Evaluation uses a mathematical approach to estimate the central tendency and high-end percentiles when the distribution of exposure samples is unknown. However, this methodology does not account for all sources of variability in exposure, nor does it account for representativeness of exposure estimates within each occupational exposure scenario. For example, the data provided by the Halogenated Solvents Industry Alliance for worker exposure during manufacturing (Evaluation, Tables 2-28 and 2-29) are based on 136 samples, coming from only 2 companies. For the manufacturing scenario, the data consists of 136 data points obtained from 1 source (Evaluation, page 115). The Evaluation should provide additional detail on these data, including the number of companies represented, conditions under which measurements were taken, etc.

- o **Recommendation 4.21:** Provide a better characterization of important exposure determinants (i.e. number of tasks/occupations, number of companies sampled, date range of samples) when describing the exposure data and exposure assessment approach in the Occupational Exposure Scenarios in section 2.4.1.2 of the Evaluation.

The Committee suggested that the Evaluation use personal monitoring data samples in OSHA (2019), as well as data provided by Finkel (2019). While the OSHA (2019) data are used for three exposure scenarios [Industrial Adhesive use (Table 2-49); Paints and Coatings (Table 2-51); and Plastic Product Manufacturing (Tables 2-71 and 2-72)] this data set includes important exposure data that can supplement exposure data used in other scenarios. Sampling data from the North American Industry Classification System (NAICS) 325199 code should also be incorporated into the occupational inhalation exposure summary metrics presented in Tables 2-28 and 2-29 of Worker Exposure to Methylene Chloride During Manufacturing. The relevant samples are summarized below in Table MC4-1. Likewise, SIC codes provided within Finkel (2019) can be matched with occupational exposure scenarios to provide additional exposure data for a number of scenarios.

- o **Recommendation 4.22:** Include sampling data provided in OSHA 2019 and Finkel 2019 to better characterize methylene chloride exposures in a number of occupational exposure scenarios.

- o **Recommendation 4.23:** Include a comparison of the exposure model predictions to the monitoring data ("Supplemental Information on Releases and Occupational Exposure Assessment", Section 4.2.3, page 123) or include an explanation as to why this was not done.

- o **Recommendation 4.24:** Include the mean and standard deviations used to define the lognormal distributions in the tables summarizing the distributions.

- o **Recommendation 4.25:** Entries in Table Apx_ F.1 (in Appendix F of "Supplemental Information on Releases and Occupational Exposure Assessment", page 270) should be clarified to better indicate that the parameter WtFrac was determined by sampling from 2

separate distributions, as indicated in the text, rather than a single a discrete distribution, as indicated in this table.

o **Recommendation 4.26:** The distribution for the exposure duration parameter in Tables Appendix F-3, F-4 and F-5 (in Appendix F of "Supplemental Information on Releases and Occupational Exposure Assessment," pgs. 280, 281 and 282) is given as being a discrete distribution; however, the text describes this parameter as being determined based on the number of operating hours per day. Both could more accurately be listed as a constant or as a calculated value based on the number of operating hours.

o **Recommendation 4.27:** Possible values of F_{abs} should be discussed when this parameter is first defined in the text. This is typically done for a number of the other parameter values.

Table MC4-1 OSHA 2019 Methylene Chloride personal sampling data to be incorporated into Tables 2-28 and 2-29 estimating worker exposures to methylene chloride during manufacturing.

Establishment Name	NAICS Code	NAICS Industry	Process	Sampling Time (min)[a]	Result (ppm)[b]	8-hour TWA	Short-Term Sample	OES	RA Table
COMPANY D	325199	All Other Basic Organic Chemical Manufacturing	Manufacturer	502		2502		Manufacturing (worker)	2-28
COMPANY D	325199	All Other Basic Organic Chemical Manufacturing	Manufacturer	433		103		Manufacturing (worker)	2-28
COMPANY D	325199	All Other Basic Organic Chemical Manufacturing	Manufacturer	13	136		Yes	Manufacturing (worker)	2-29
COMPANY D	325199	All Other Basic Organic Chemical Manufacturing	Manufacturer	41	58		Yes	Manufacturing (worker)	2-29
COMPANY D	325199	All Other Basic Organic Chemical Manufacturing	Manufacturer	471		47		Manufacturing (worker)	2-28
COMPANY D	325199	All Other Basic Organic Chemical Manufacturing	Manufacturer	447		18		Manufacturing (worker)	2-28
COMPANY D	325199	All Other Basic Organic Chemical Manufacturing	Manufacturer	15	ND		Yes	Manufacturing (worker)	2-29
COMPANY D	325199	All Other Basic Organic Chemical Manufacturing	Manufacturer	15	659		Yes	Manufacturing (worker)	2-29

[a] Full-shift sampling times were combined. [b] Individual sampling results available from original data source.

Q 4.2	**Please provide any specific suggestions or recommendations for alternative data or estimation methods that could be considered by the Agency for conducting the occupational exposure assessment.**

For the acute exposures, the Evaluation should consider shift lengths beyond 8-hours. The sampling data provided by the Halogenated Solvents Industry Alliance presents full-shift personal samples for as long as 12 hours. Longer exposure periods should be considered for the high-end exposure scenarios. This is relevant to each exposure scenario as well as to the calculation of the acute exposure concentration (Evaluation, equations 2-4 and 2-5) as it relates to exposure duration, and averaging time. The U.S. Bureau of Labor Statistics provides industry specific data on weekly hours worked, which on average are beyond 40 hours for the manufacturing industry (BLS, 2019).

- o **Recommendation 4.28:** For high-end acute exposure scenarios, the evaluation should incorporate longer shift lengths (exposure periods) informed with data from the HSIA surveys.

Likewise, for chronic exposure, the Evaluation should consider extended working years as workers continue to work past the traditional retirement age. The U.S. Bureau of Labor Statistics indicates that the labor force participation rate continues to increase fastest for the oldest segments of the population — most notably, people ages 65 to 74, and 75 and older. Employed persons, by occupation and industry and age is provided by the U.S. Bureau of Labor Statistics and can be used to inform industry specific working age for chronic exposure calculations (BLS, 2019).

- o **Recommendation 4.29:** For chronic exposure, extended working years should be factored into the assessment, since workers continue to work past the traditional retirement age.

A Committee member pointed out a caveat with respect to addressing values reported as non-detect in that there are different approaches for handling these values beyond replacement by ½ the detection limit, 0, or the detection limit. The selection of non-detect replacement method can affect estimates of central tendency and 95th percentiles. A substantial body of literature on the treatment of non-detects for estimating population parameters has been developed over the last few decades, including studies and guidance by EPA for various applications as well as by other Agencies. The EPA should consider these methods. As a start, Helsel (2010) provides a critical review of some methods for dealing with non-detects.

Committee discussions touched on the following issues:

- o **Recommendation 4.30:** State environmental and health agencies can be queried about the availability of monitoring and exposure data relevant to this chemical. These data should be obtained and incorporated into the assessment. Washington State was mentioned as likely having such data that could be shared.

- o **Recommendation 4.31:** Consider OSHA violation reports on glove and respirator use which may provide data on the frequency or extent of usage in the industry.

- o **Recommendation 4:32:** The Evaluation should highlight those scenarios where safety margins are absolutely dependent on proper PPE usage.

- o **Recommendation 4:33:** GSTT1genotype plays an important role in individual response to methylene chloride exposures. This defines (genetically and proportionately) a specifically susceptible subpopulation that should be further discussed in the Evaluation.

- o **Recommendation 4.34:** The Evaluation should define and assess worker subpopulations that would be expected to have enhanced inhalation intake, such as tobacco smokers.

- o **Recommendation 4.35:** Committee members suggested that EPA not refer to the 95th percentile value as a 'high-end estimate' of exposure. It is misleading to suggest that the 95th percentile value is an upper bound on exposure since exposure distributions are typically skewed and as a result, higher percentile values, e.g. the 99th percentile value, can often be an order of magnitude or higher than the 95th percentile value.

- o **Recommendation 4.36:** The exposure concentrations for PUF manufacturing are highly variable (Tables 2-65 and 2-66). Therefore, a clearer presentation of resulting uncertainty in exposure estimates is important.

Q 4.3	**EPA assumed the following default surface area value for modeling dermal exposures for occupational exposure scenarios for which surface area data were not available: a high-end value of 1070 cm^2, which represents two full hands (mean value for males) in contact with a liquid. Please provide input on data sources and specific alternative values relevant to the uses.**

Response:

The assumption of two full hands in contact with the liquid is appropriate and conservative (particular for female workers who have smaller hands). However, EPA should indicate why an upper bound for hand surface area was not used. The potentially exposed surface area was obtained from The Exposure Factors Handbook (EPA, 2011), with percentiles of hand surface area derived from National Health and Nutrition Examination Survey (NHANES) data, so it can be considered a robust estimate. The Agency should indicate how the dermal exposure and risk evaluation would have changed had they decided to use an upper percentile value for hand surface instead of the average. The Agency clarified at the face to face meeting, that this area likely represented more than just hand surface. The Agency limits dermal exposures in the high-end scenario to two hands. One Committee member noted that exposure to the forearm is likely.

Industrial facilities often lack air conditioning and workers often wear short sleeves shirts. Exposure to the forearm likely occurs among these individuals.

- o **Recommendation 4.37:** Expand the discussion of hand surface area to more adequately describe the exposed surface and include dermal exposure to forearm to better describe the high-end exposure scenarios.

The Agency does not address the vapor through the skin dermal exposure pathway, including through clothing fabrics. This pathway should be mentioned, and EPA should indicate why it was not considered. Exposure to methylene chloride vapor directly or through clothing could add to dermal exposure estimates from direct contact with the liquid. In addition, fabric impermeability to the liquid phase does not necessarily guarantee impermeability to the vapor phase. Both the American Society for Testing and Materials - International (ASTM-International) and the National Fire Protection Association (NFPA) test and provide guidance on liquid and vapor penetration through fabrics for many chemicals, particularly fabrics used in protective clothing. EPA should contact these organizations about test data for penetration of methylene chloride vapor (and for other chemicals EPA is evaluating now and will in the future) and revise the sources of dermal exposure appropriately, if needed. At a minimum, this potential route of exposure for OUs and ONUs should be mentioned. (See Recommendation 4.18).

- o **Recommendation 4.38:** Discuss the potential for the vapor-through fabric dermal exposure route and incorporate it in the dermal exposure estimates if suitable data are available to estimate the contributions to exposures.

While Section 4.3.7 discusses in general terms the uncertainties related to inhalation exposures assessment, there is no discussion of uncertainties related to dermal exposure; either data or model derived.

- o **Recommendation 4.39:** Include a discussion of uncertainty related to dermal exposure assessment in Section 4.3.7 of the Evaluation.

Facilities with fewer than 10 employees are not required to report to TRI. The Committee wondered whether the manufacturers and processors data in the National Pollutant Discharge Elimination System (NPDES) permit system could provide estimates on the number of facilities having under 10 employees. These data could be used to estimate the degree of underestimation in the current assessment.

- o **Recommendation 4.40:** Consider using NPDES data to estimate the number of facilities employing fewer than 10 workers and use these data to assess the potential degree of under-estimation in the current assessment.

To estimate ONU inhalation exposure, EPA reviewed personal monitoring data, area monitoring data and modeled far-field exposure concentrations. When EPA did not identify personal or area data or parameters for modeling potential ONU inhalation exposures, EPA assumed ONU inhalation exposures could be lower than worker inhalation exposures, however relative exposure of ONUs to workers could not be quantified. When exposures to ONUs were not quantified, EPA considered the central tendency from worker personal breathing zones to estimate ONU exposures.

Q 4.4	**Please comment on the assumptions and uncertainties of this approach.**

Response:

Overall, the Committee agreed that the assumptions made in the assessment of ONU exposures are scientifically sound. The Agency describes clearly the uncertainties inherent in their approach for estimating ONUs exposures. However, reliance on the assumption that assigning workers' central tendency exposures is conservative (because such exposures are likely to be lower) should be tempered. As indicated in the previous section, ONUs are likely a heterogeneous population of workers, and some could be exposed more than just occasionally to high concentrations. This possibility should be included explicitly as a source of uncertainty. As recommended earlier, EPA should consider the different categories of ONUs potentially at risk from exposure to methylene chloride at the different conditions of use. It could then develop a set of ONU-related scenarios and attempt to model their exposures.

The Committee noted that in Section 2.4.1.2.2 (Evaluation, page 117, lines 2114-2119), area monitoring data were available, but were not used. Instead modeling was used to estimate ONU exposures. No comparison of measured to modeled exposure estimates for ONUs is offered in the Evaluation.

- o **Recommendation 4.41**: Monitoring data should have been compared to the modeled estimates and justification provided if it is not possible to do a comparison. Additional discussion is needed on the representativeness or lack thereof of the data. When both monitoring and modeling estimates are available, the most conservative estimate should be used.

The Committee expressed concerns that unless use of methylene chloride is physically sequestered from other methylene chloride-releasing jobs in the same area, the assumption that ONUs are less exposed than users is not sufficiently supported.

- o **Recommendation 4.42**: The Evaluation should expand the descriptions to show physical sequestration of methylene chloride from other sources in the same work area or add uncertainty factors for these scenarios where more than one user is present.

In the discussion of ONU exposure, the Committee also discussed the following issues briefly but provided no firm recommendations.

- o The need to aggregate exposures through multiple routes and perform a risk evaluation on overall exposure, not only components through specific routes.

- o The need to assess and indicate whether one route of exposure is clearly more important than another in order to prioritize mitigation approaches.

- o The need to determine and describe occupational exposure scenarios where the industry standard is to provide dedicated ventilation.

- o Several Committee members suggested EPA assume 8-hours of exposure duration for central tendency worker and ONU.

Q 4.5	**Are there other approaches or methods for assessing ONU exposure for the specific condition of use?**

Response:

Consumer exposure estimates were developed for the conditions of use for inhalation and dermal exposures to consumers. The Agency did a systematic review, collected data from available sources and conducted modeling for estimating consumer inhalation and dermal exposures using the Consumer Exposure Model (CEM).

Product specific consumer monitoring information was not identified during the systematic review process, therefore, model inputs related to consumer use patterns (duration of use, mass of product used, room of use, and similar inputs) are based on survey data found in the literature as described and referenced within the methylene chloride draft risk evaluation. Weight fractions of the chemical within products are based on product specific safety data sheets (SDSs). Default values utilized within the models are based on literature reviewed as part of model development as well as EPA's Exposure Factors Handbook.

The Agency could explore using modeling for estimating ONUs exposures. Models used in industrial hygiene (AIHA, 2009) could be adapted for this purpose using assumptions based on professional judgment and input from users.

While exposure data for ONUs is sparse, the assumption that the representative exposure level for ONUs is best determined as the central tendency (mean/median exposure) for occupational users is unsupported. A better estimate discussed by the Committee is one that uses the estimated distance of ONUs from users and the inverse square law to compute the estimate. Air exchange rates would need to be accounted for in any case.

- o **Recommendation 4.43**: The Evaluation should examine how ONU risk changes if exposure is estimated using the distance from ONUs to users and the inverse square law.

The Committee had no further comments or additional recommendations for this question.

Consumer exposure estimates were developed for the conditions of use for inhalation and dermal exposures to consumers. EPA did a systematic review, collected data from available sources and conducted modeling for estimating consumer inhalation and dermal exposures using the CEM.

Product specific consumer monitoring information was not identified during the systematic review process, therefore, model inputs related to consumer use patterns (duration of use, mass of product used, room of use, and similar inputs) are based on survey data found in the literature as described and referenced within the methylene chloride draft risk evaluation. Weight fractions of the chemical within products are based on product specific SDSs. Default values utilized within the models are based on literature reviewed as part of model development as well as EPA's Exposure Factors Handbook.

Q 4.6	Please comment on the approaches, models, exposure or use information and overall characterization of consumer inhalation exposure for users and bystanders for each of the identified conditions of use. What other additional information, if any, should be considered?

Response:

The modeling methods and assumptions appear appropriate, considering the lack of data. The assumption of no use of PPE for consumers is also appropriate. The CEM is peer-reviewed and, based on the Evaluation, default parameters were used for the CEM for all but 3 parameters, which were product-specific. The decisions are appropriate for these 3 parameters for the specific products being modeled. However, EPA should consider carefully the assumption that the bystander(s) will remain in a different room (Zone 2 for the purpose of modeling) during use of a product. Depending on the actual use, product, and specific application, the assumption of far-field location for the bystander(s) during use may not be sufficiently conservative. For example, a carburetor cleaner will likely be applied inside a garage (or outdoors) with only the user present. Alternatively, this may not be the case with adhesives and adhesive removers, which could be applied in any room within a residence. At a minimum, EPA should specifically address the uncertainty about bystander location depending on specific product use.

As indicated in the Evaluation, the CEM assumes zero baseline concentration of methylene chloride. Despite not considering aggregate exposures, EPA should indicate that this assumption is not conservative because population exposure data (which EPA presents in the Evaluation) show that there are measurable concentrations of methylene chloride in the indoor air of homes as well as in the personal breathing zone of the occupants. This is in part explained because there are emission sources of methylene chloride to ambient air, which infiltrates homes; domestic water (which is used indoors); tobacco smoke that contains methylene chloride, and methylene

chloride containing consumer products that are stored in homes or attached garages, in addition to the occasional use of these products. On the other hand, blood concentrations of methylene chloride were undetectable in 2,878 individuals measured as part of the 2009-2010 NHANES. These findings are not discussed in detail in the Evaluation and these observations should be better explained. This also suggests that chronic exposure modeling for consumer exposure should also be included in the risk evaluation.

- o **Recommendation 4.44**: The potential exposures of the general public to methylene chloride need to be clarified further.

The Agency does not consider that there is an increasing number of people that engage in activities using products, such as adhesives, more frequently and for longer periods than the typical occasional user. This sector of the population straddles the worker/hobbyist category in that they engage in these activities more intensively for profit and/or for pleasure. The Agency should recognize that this is a sector of the population that may be at higher risk from exposure than the typical consumer. The Agency should consider developing methods for assessing the size and risk from exposure for this subpopulation.

The Agency presents information on indoor and personal air concentrations of methylene chloride for residential homes and occupants (Evaluation, Section 2.4.2.5). This had not been done in prior TSCA evaluations reviewed by the Committee DREs. The Committee supports presenting these data, when available, because it provides a context for at least some of the general population exposures which can be compared to product use-related exposures. The data provided by EPA is incomplete. As part of the Total Exposure Assessment Methodology (TEAM) studies, EPA measured concentrations of methylene chloride in residential indoor and exhaled breath (Wallace et al., 1991) before the lowering of the PEL in 1997. The Agency and the Health Effects Institute (HEI, Boston, MA) also sponsored the Relationship between Indoor, Outdoor, and Personal Air (RIOPA) study (Weisel et al., 2005a, b, c). This study included monitoring of indoor, outdoor, and personal breathing zone concentrations (for one adult occupant and children who consented to participate) of VOCs, including methylene chloride, airborne aldehydes, PM2.5, and selected polycyclic aromatic hydrocarbons (PAHs) for approximately 100 homes each in Elizabeth, NJ; Los Angeles, CA; and Houston, TX, during two different seasons each. The Agency has the database for this study, which also includes residential air exchange rate measurements, indoor/outdoor temperatures and relative humidity values, and household and individual participants' activity patterns (EPA, 2019). Phillips et al. (2005) also monitored indoor and personal air for selected VOCs, including methylene chloride, in four Oklahoma cities.

Note that Pratt et al. (2005) reported method detection limits for methylene chloride that are representative for the studies by Adgate et al. (2004) and Sexton et al. (2007) because measurements were made with the same sampler and sampling/analysis protocol, and the analysis was performed by the same laboratory in all these studies. These values could be reported in Tables 2-120 and 2-121 (Evaluation, pages 194-195) with an appropriate footnote.

Most products were parts cleaners, adhesive, adhesive removers, insulation spray, and were primarily available in aerosol form, with some products available as liquids. Consequently, inhalation exposure was deemed the most relevant for consumers, since the liquid forms of methylene chloride are expected to lead to inhalation exposure due to methylene chloride's high vapor pressure. Inhalation exposures were evaluated for both consumer and bystander, while dermal exposure was evaluated for consumers only. It seems logical to consider ingestion exposure as unlikely. The amount of chemical in the models included ranges (minimum and maximum) to take into account uncertainties in the percentage of methylene chloride noted in a particular product (e.g. <40%).

Since consumer use seems limited to occasional exposure, it is unclear why methylene chloride has been routinely detected, albeit at low concentrations, in evaluations of indoor air of residential homes in the U.S. and Canada. However, personal breathing zone data indicates there is personal exposure to methylene chloride, including in children.

- o **Recommendation 4.45**: The potential exposure of the general public to methylene chloride needs to be clarified and/or expanded.

In Section 3.2.5.2 of the Evaluation where the derivation of PODs is described (in the human hazard section), there's a statement that; "A 1-hour value is used for consumer settings, which is similar to the length of time (1.5 hours) after which effects were observed by Putz et al., (1979)." One hour seems too short to estimate consumer exposures, even just based on the few fatality case studies described in Appendix J – Case Reports of Fatalities Associated with Methylene Chloride Exposure. But in some places in the Evaluation, in estimating consumer exposure for specific uses, different time lengths were used, hence the Evaluation does not rely exclusively on the 1-hour assumption for everything.

- o **Recommendation 4.46**: The exposure time for consumer exposures for all uses (scenarios) should be detailed in Section 3.2.5.2 or in an associated Appendix/Supplemental file.

Table 2-121 appears to reference the Adgate, et al. (2004) study twice as the corresponding text refers to only two studies and the Adgate study rows only differ by the Detection Frequency (DFq) values.

One Committee member was unclear as to how the brush cleaner condition of use (COU) was defined. Subsequent discussion indicated that this is a COU that was not considered in 2014 risk evaluation, and which has much lower use percentages and differing use patterns when compared to paint removers/strippers into which EPA categorizes this product. This is significant since it was the only consumer COU that met the "does not present an unreasonable risk" criteria.

- o **Recommendation 4.47** Clearly define the brush cleaner COU in the Evaluation.

Many of the links noted in the Use and Market Profile for Methylene Chloride (EPA 2017) were observed by Committee members to no longer be active or to describe products that no longer contain methylene chloride.

- o **Recommendation 4.48**: Reconfirm the Use and Market Profile products links and update profiles, eliminating products that no longer contain methylene chloride.

One Committee member mentioned that while methylene chloride is a solvent that may be used in some children's product manufacturing processes (e.g. metal component degreasing, solvent bonding, paint/ink carriers), due to its high volatility, significant concentrations are unlikely to remain in products as received by consumers. It appears that some manufacturers are reporting this substance under state reporting statutes at concentrations of up to 10,000 ppm. The informed Committee member considered reported concentrations this high are very unlikely to be accurate, and instead reflect over-reporting, which is common.

Several Conditions of Use (COU) described under both Consumer and "Industrial and Commercial" were not evaluated under Consumer uses. This was also noted in the written comments (page 16) presented by the Environmental Defense Fund and included in the docket.

- o **Recommendation 4.49**: Ensure that these COU do not exist in the Consumer space and evaluate the COU if they are reasonably foreseen to exist.

One Committee member noted that a comprehensive accounting of methylene chloride in consumer products may be obtained from the California Air Resources Board which collects this information, including weight-percent and estimated emissions. The Committee member provided a summary of these data to EPA for the docket.

Q 4.7	**Please comment on the approaches, models, exposure or use information and overall characterization of consumer dermal exposure for each of the identified conditions of use. What other additional information or modeling approaches, if any, should be considered?**

Response:

Comments presented above regarding occupational dermal exposure and absorption are also generally applicable to consumer dermal exposure and absorption. Current approaches require further clarification and justification.

The Committee expressed concern that the dermal surface area for exposure indicated in Table 2-88 seems low – 10% for activities that involve spray and inside of both hands for some of the cleaning surveys. The only justification of this assumption is provided in footnote 6, page 176 of the Evaluation, which indicates "Selected dermal SA/BW ratio used is based on CEM scenario used or best professional judgment for Generic Scenario." The justification for this assumption would be strengthened by including additional supporting information, including but not limited to an indicator of which scenarios use dermal surface area based on the CEM scenario and which are based on professional judgment. The justification should also discuss whether the dermal surface area of exposure assumptions include dermal exposure from the product application as well as dermal exposures through rags containing product or spills on clothing, which likely occur in these consumer scenarios and which could increase the dermal surface area to which

consumers are exposed.

- o **Recommendation 4.50**: Document the dermal surface area assumed for each occupational COU exposure scenario, indicate which estimate is based on CEM and which based on best professional judgment, and indicate whether the dermal exposure estimate includes application exposures, rag exposures and spills to clothing.

Q 4.8	**Dermal exposure was evaluated using the absorption method submodel within CEM. Please comment on the suitability and use of this modeling approach for this evaluation. Please provide any suggestions or recommendations for alternative approaches, dermal methods, models or other information which may guide EPA in developing and refining the dermal exposure estimates.**

Response:

The Committee found the dermal models available within the consumer exposure model (CEM) appropriate and, given how these products are used, dermal exposure is likely. There were however several issues arising from concerns previously noted that suggest other actions and information that could be used to refine the analysis of dermal exposures. These actions and other information are outlined in the following recommendations, recognizing that addressing these may require further research and/or data collection.

- o **Recommendation 4.51**: The hierarchy of approaches to exposure estimation is not always appropriate. The Agency should develop a protocol for deciding when measurement data of good quality are available in sufficient quantities to derive reliable estimates. If they are not sufficient, modeling could be a preferable approach to available measurements.

- o **Recommendation 4.52**: Consider exploring different categories of ONUs and develop scenarios for conditions of use that are amenable to modeling their exposures using assumptions informed by professional judgment and/or information provided by users.

- o **Recommendation 4.53**: Indicate clearly whether all proactive venues for obtaining necessary and/or missing information (including uses, PPE, or specific information on monitoring samples) were exhausted and whether indeed there was no way of obtaining these data.

- o **Recommendation 4.54**: Describe in a transparent manner how EPA derives data quality ratings and overall confidence levels, so it is clear how uncertainties are reflected into these evaluations.

o **Recommendation 4.55**: Describe the potential of the vapor to the skin exposure route, including penetration of the vapor through clothing fabrics.

o **Recommendation 4.56**: Reconsider whether bystanders are always located in a different zone than the user for the consumer use scenarios, independent of the type of product.

o **Recommendation 4.57**: Recognize that a sector of the population could be at increased risk from exposure than the typical consumer because they engage in hobby-type activities for both pleasure and profit. Essentially, they could be considered home-based workers.

Question 5: Human Health Hazard:

EPA used the acute point of departure (POD) to use to estimate risks from the human controlled experiment described by Putz et al. (1979). This study was rated as a medium quality study; it was a double-blind design but used a single exposure, which prevented the use of dose-response modeling. Given uncertainty regarding concentrations and exposure durations and the potential for a steep dose-response leading to death as suggested by these case reports and the analysis by Benignus et al. (2011), EPA considers Putz et al. (1979) to be the most relevant study for this risk evaluation.

Q 5.1	Please comment on the appropriateness of the approach, including the data quality evaluation, and the approach's underlying assumptions, strengths and weaknesses.

Response:

The use of Putz et al. (1979) for the POD derivation and central nervous system (CNS) effects was generally accepted by the Committee as the relevant endpoint for acute toxicity in humans. The Committee found the use of human data for the POD appropriate as was the use of animal model results in the weight of evidence (WOE). Putz et al. is a good human study that examined auditory and visual effects caused during a 4-hour exposure to 200 ppm methylene chloride, which was used to approximate a normal 8-hour workday with exposures to 100 ppm methylene chloride. The Committee agreed that Putz et al. cannot be used for dose-response modeling because it does not evaluate multiple doses. It can, however, be used to define a lowest observe adverse effect level (LOAEL) for use as a POD. Putz et al. (1979) cites earlier studies (Gamberale et al 1975, Winneke et al. 1974) that evaluated multiple doses as the justification for using a single dose. The Evaluation appropriately places this single-dose study in the context of other studies that provide data on dose-response.

The Committee questioned the conclusion in the Evaluation that the methylene chloride-induced CNS effects are concentration-dependent with a steep dose-response curve. This conclusion would be strengthened by considering the exposure response of CNS effects from other similar

quality studies reviewed. For example, Winneke et al., (1974) included multiple measures of CNS effects in larger sample sizes than Putz et al. (1979) and included five exposure concentrations ranging from 50 ppm to 800 ppm. One Committee member noted that a steep dose-response curve is very unlikely given the well-established toxicokinetics for methylene chloride (i.e., rapid approach of near steady-state) of inhaled methylene chloride in humans (Bos et al., 2006). The prediction from Benignus et al. (2011) that the frequency of fatal car accidents may increase at exposures less than one ppm is questionable, and data from other studies included in the Evaluation could be used to establish a LOAEL of 200-300 ppm. The Evaluation misinterpreted the rationale of NAS (2009) in setting its 8-hour acute exposure guidance level (AEGL)-2 at 60 ppm. Decrements in performance in humans inhaling up to 751 ppm for 230 minutes were not considered severe enough to significantly impair one's ability to escape a dangerous environment, and thus were not used as the basis of the AEGL-2 derivation. The values were instead based upon PBPK model simulations of carboxyhemoglobin (COHb) levels at selected exposure times.

The question on data quality resurrected previously discussed issues on absolute data quality, relative data quality, and issues with the systematic review process. Unlike with previous draft risk evaluations, there was no specific charge question for assessing the systematic review of this chemical. While data quality criteria for human studies are not included in the Agency's Application of Systematic Review in TSCA Risk Evaluations (USEPA 2018), the narrative evaluation for the human studies and the included scores in Table 3-3 (Evaluation, page 225) were appreciated. The Committee noted that both the Putz et al. (1979) and Winneke et al. (1974) studies were rated as "Medium" for data quality for minor issues, especially when compared to the rankings of other sources of information.

- o **Recommendation 5.1**: Use the data from the Winneke et al. (1974) study to confirm the assumption used in the dose-response modeling of the Putz et al. (1979) study.

The use of the human studies for POD again highlighted how standards across types of studies should be applied more uniformly. Minor issues with studies deemed relevant to human health hazard can lead to a rating of "unacceptable" while studies for other topics (examples in Table 1-1, Evaluation page 39) that have no mention of methods are rated "low" for that criterion, yet end up being rated "high" overall.

Discussion indicated that there are several definitions of "unacceptable," and different Committee members use or envision this term differently. The Agency's use of "unacceptable" relates to how the results of a study are used in the WOE argument. The Committee noted that the criteria for human health studies in animal models are disproportionately stringent, since use of a single dose, as done by Putz et al. (1979), would rate such a study as unacceptable. The Committee raised these issues previously, and the Committee again recommends improvement of the systematic review process, including the definition and use of "unacceptable" studies in TSCA risk evaluations. The Committee reiterates that single dose studies can contain useful information and should not be ranked "unacceptable" just for having a

single dose. The Committee appreciated that some new definitions for the systematic review were included with this Evaluation.

- o **Recommendation 5.2:** Develop quality assessment criteria for human studies to be included in its systematic review methods prior to review by the National Academy of Sciences (NAS) and make other improvements to the systematic review as previously detailed, including the definition and uses for "unacceptable" studies.

Limitations in the evaluation of epidemiological studies and the "healthy worker effect" were noted. In section 3.2.4 at the beginning on line 6027 (Evaluation, page 264) on evaluating limitations of epidemiological studies, an incomplete description and analysis is given to a series of biases collectively called the "healthy worker effect." Within the limitations described under point 1, the healthy hire bias which occurs when comparing dissimilar groups (workers versus the full population) is acknowledged. However, the other biases, namely the healthy worker survivor bias, can occur when workers with poorer health status continue to leave the workforce or switch jobs and as a result incur lower exposures. Stated another way, when the occupational exposure of interest has an effect on health, it may also affect employment status (Buckley 2015, Brown 2017). Unlike the healthy hire bias, this cannot be addressed using internal reference groups. Furthermore, as indicated in Brown et al. (2017) "If occupational data are not analyzed using appropriate methods, this bias can result in attenuation or even reversal of the estimated effects of exposures on health outcomes." This lends further credence to the statement found on page 265 line 6043 of the Evaluation: "However, it is possible that the effects of methylene chloride could be masked in these cohorts that use dissimilar comparison groups."

- o **Recommendation 5.3:** Add further details to the evaluation of the epidemiology studies to fully describe the "healthy worker effect."

Q 5.2	Please provide any specific suggestions or recommendations for alternative approaches that should be considered by the Agency in characterizing the acute inhalation risks.

Response:

The Evaluation does not make full use of the available data on methylene chloride's human acute lethality. Methylene chloride has been linked to more than 60 deaths nationwide since 1980 (ref: Safer Chemicals, Healthy Families). One Committee member suggested that the few case reports in Appendix J address this issue insufficiently.

- o **Recommendation 5.4:** Increase use of the human lethality data.

- o **Recommendation 5.5:** Use PBPK model for acute exposures or provide justification as to why the PBPK model is not suitable for acute exposures in the Evaluation is warranted if that is what is determined.

Q 5.3	**Please provide relevant data or documentation and rationale for including other studies and endpoints for consideration.**

Response:

The Committee considered the potential immunotoxicity of methylene chloride to be underestimated, even based on the somewhat equivocal results. As included in the Evaluation, there are a few epidemiological studies that show a weak association, and this is supported with data from short-term animal models. The evidence, especially the results from Arayni et al. (1986), fulfill the National Toxicology Program (NTP) criteria for "clear evidence of toxicity to the immune system (NTP 2009)." Warbrick et al. (2003) showed no effect of methylene chloride exposure in rats on IgM anti-SRBC antibody production. However, the anti-SRBC response is more robust than almost any other supposedly T cell-dependent antibody response, and it is not clear that it would be particularly sensitive to immunosuppression. Two-year inhalation and oral studies did not identify histopathological changes in lymph nodes, thymus or spleens in rats. However, these results are not in any way conclusive; many robust immunomodulatory effects produce no changes in tissue histopathology. Unlike these other studies, the study conducted by Arayni et al. (1986) investigated a functionally relevant outcome following methylene chloride exposure. This study evaluated more than one measure of immune response in female mice exposed by inhalation to one of 14 different chemicals. The mice were simultaneously exposed to aerosolized *Streptococcus zooepidemicus*. Most of the chemicals, including acetaldehyde, acrolein and carbon tetrachloride, did not increase mortality in response to the microbial challenge. In contrast, a single inhalation exposure to 100 ppm methylene chloride significantly increased mortality following the microbial challenge and generated an associated decrease in the bactericidal activity of alveolar macrophages. The Arayni et al. study, which included EPA investigators, was not rated more highly because of a lack of information about test substance preparation and animal group allocation. The Committee disagrees with this rating. Accidental bias on group allocation (e.g. most of the smaller animals ending up in one group) is more of an issue when the groups have a small number (N) of animals, and seem much less of a possible confounding factor when the groups have an N=140 mice, as is the case for the Arayni et al. study. In addition, the experimental design of the study largely conformed to the tiered approach (with microbial challenge) to immunotoxicity testing advocated by the NTP (2009). NTP has five levels to compare the strength of the experimental evidence for immunotoxicity. The top level "Clear Evidence of Toxicity to the Immune System" is demonstrated by "data that indicate dose-related effects on one functional assay and additional endpoints that indicate biological plausibility."

- o **Recommendation 5.6:** Add a conclusion statement to section 3.2.3.1.3 Immune System Effects stating that this summarizes the equivocal results while acknowledging the strong potential for methylene chloride immunotoxicity based on the Aranyi et al. (1986) study.

One Committee member commented that not including irritation and burns isn't protective of human health and noted an additional source of information. King County, Washington analyzed poison center data for 2007-2016 for methylene chloride (Fisk and Whittaker 2018). If further information is needed, the Agency should contact Dr. Whittaker for the case reports.

- o **Recommendation 5.7:** Include more information on irritation and burns.

The Committee commented that exposure via breast milk was not considered and discussed what data exist. One Committee member noted another reference by Fisher et al. (1997) that should be included. This topic was further discussed later in regard to the PBPK model.

Q 5.4	**Please comment on the severity of the response used as the basis of the POD as well as the use of the result at 1.5 hours rather than at 4 hours.**

Response:

The Committee was satisfied with this approach and further commented that the Putz et al. (1979) study identified effects at a concentration (195ppm) not studied by others. The CNS effects were upstream of more severe pathology at higher concentrations, and it identified effects (peripheral light response time) as early as 1.5 hours after the initiation of exposure. The CNS effect in this study were concentration- and time-dependent supporting an exposure duration adjustment to 15-min, 1-hour and 8-hour is appropriate. Given the more or less linear dose-response relationship for methylene chloride-induced effects, this provides support for using the 1.5-hour exposure for the exposure duration adjustment to 8-hour. The Committee suggested the Evaluation should support conclusions by including data from other human studies measuring CNS effects from longer duration exposures than are summarized in this risk evaluation.

- o **Recommendation 5.8:** EPA should use the data from the Winneke et al. (1974) study to confirm the assumption used in the dose-response modeling of the Putz et al. (1979) study.

One Committee member disagreed with the EPA's decision to use what was characterized as a negligible biological effect of highly questionable significance (i.e., a 7% decrease in visual peripheral performance (VPP)) at 1.5 hours as the basis for the POD for acute/short-term inhalation exposure to methylene chloride. The 4-hour exposure to 195 ppm methylene chloride still resulted in only a 17% decline in VPP, but a 36% decrease in eye-hand coordination. The Committee member felt that these modest CNS effects are more useful in establishing a LOAEL and recommended the Agency use the 4-hour exposure level of 200 ppm to convert to the 15-minute, 1- and 8-hour PODs. The Committee noted NAS/AEGL (2009) used a 1-hour human no observed adverse effect level (NOAEL) of 514 ppm as its POD for derivation of its AEGL-1.

For methylene chloride, exposure-versus-time data are limited. Therefore, EPA considers the Ten Berge equation using n = 2 as a valid method to convert the 1.5-hour POD value from Putz et al. (1979) to the 15-min, 1-hour and 8-hour PODs.

_Q 5.5_	**Please comment on the conversion of the 1.5 h time point in Putz to 15 min, 1-hour and 8-hour PODs.**

Response:

Several Committee members suggested use of the PBPK model for estimating the acute exposures. The Agency used the PBPK model for the chronic inhalation exposures and NAS (2009) used the PBPK model for deriving the AEGLs. The Committee described the PBPK model as both more scientifically justifiable and more protective of human health.

One committee member supported the use of the Ten Berge equation but noted there are additional relevant models. Committee discussion pointed out that the Ten Berge equations have limitations. The work of Ten Berg (1986) was limited to data on lethality and often does not accurately reflect dose-response relationships for very short periods of exposure, as well as for longer durations (Bruckner et al., 2004). Use of the C^nxt approach can underestimate longer AEGLs and thereby overestimate risks. NAS (2009) utilized PBPK modeling extensively for time scaling in its calculation of AEGLs for methylene chloride. Bos et al. (2006) also utilized this approach to derive AEGLs.

Additional advantages were identified for using PBPK modeling over the Ten Berge equation. It should be recognized that blood and brain concentrations of methylene chloride increase rapidly upon initiation of inhalation exposure, approaching near steady-state, or equilibrium within 1½-2 hours. CNS depression is directly attributable to the parent compound. Human PBPK modeling and monitoring data show gradual, progressive increases in blood methylene chloride levels over the next 6 hours of exposure (Bos et al., 2006). For duration adjustments NAS (2009) used a PBPK model based on a modification of the model of Andersen et al. (1987, 1991) and by Reitz et al. (1997). NAS (2009) utilized the same modeling to simulate COHb levels for derivation of AEGL-2 values.

   o **Recommendation 5.9:** Use the PBPK model to estimate acute exposures or justify why it is not suitable for this task.

One Committee member identified problems with reproducing calculations and noted that reported values may have been rounded. The one-hour POD was calculated as 238.9 ppm rather than the 240 ppm reported, but this is not likely an impactful difference. However, calculations for the 8-hour POD produced 84.4 ppm rather than 80 ppm and noted this may make a difference. It is not clear to the Committee why these results are different when using the same formula referenced in the report suggesting that calculations need to be checked.

o **Recommendation 5.10:** Check calculation for 1 hour and 8-hour POD to ensure no impactful rounding is occurring.

EPA used PODs and cancer slope factors (i.e. human equivalent concentration (HEC), inhalation unit risk (IUR) and dermal slope factor) for evaluating the non-cancer and cancer risks, respectively, for chronic exposures to methylene chloride.

$Q\ 5.6$	**Please comment on the appropriateness of the approach, including its underlying assumptions, strengths and weaknesses.**

Response:

Committee members found liver effects reasonable as the most sensitive non-cancer endpoint and supported by evidence, although questioned parts of the approach and requested additional explanations.

It was suggested that the National Research Council (NRC) recommendations to use Bayesian uncertainty factors in the development of criteria for risk assessment purposes (Evaluation, line 6252, Table 3-17 and elsewhere) be considered as an alternative approach.

o **Recommendation 5.11:** Consider using the NRC recommendations and use Bayesian Uncertainty Factors in the development of criteria for risk assessment purposes.

The Evaluation needs to justify why its analysis approach differs from the EPA's National Center for Environmental Assessment (NCEA) recommendation to use trend tests over pairwise tests for assessing the significance of less common health effects (page 9 in "Supplemental Document on Benchmark Dose and PBPK Modeling"). The Committee wondered why this isn't mentioned in the main text.

One Committee member questioned use of body weight scaling on animal $BMDL_{10}$ predictions. This scaling factor seems to be used to account for uncertainty in the amount of time the active metabolites might actually be in the tissue of animals versus humans. Since the model does not track the pharmacokinetics of these active metabolites, the best dose metric available, given the accepted MOA is the amount of methylene chloride metabolized by GSTT1. Given that there is uncertainty regarding differences in clearance, then it seems that using an uncertainty factor of 3 for pharmacokinetic differences would be a more consistent approach to addressing this uncertainty. Even if body weight scaling is used, it should be applied after the model is used to get the human external doses since this entire process of using modeling is based upon calculating human external doses based on matching human and animal internal doses. Given that these models may or may not be linear in the region of these doses, when the scaling factor

Page **57** of **88**

is applied could make a difference in the risk estimates. It would be useful if more detail was added on how the sampling for the GSTT1 polymorphism was conducted (Appendix I, page 659, lines 11601-11603).

The selection of a LOAEC-to-NOAEC uncertainty factor (UF) of three was not well justified. The reasons for reducing the UF from ten to three based on the magnitude of the effect was unclear, and the Committee noted that other agencies have not done this (e.g., the California Office of Environmental Health Hazard Assessment (OEHHA) used 6). One Committee member suggested that a LOAEC to NOAEC UF was not needed, since the observed effect (7% decrease) was essentially a NOAEC. The Committee questioned why a database UF wasn't included, even if it is not historically used in TSCA evaluations.

The Committee noted there is no charge question on potentially exposed and susceptible subpopulations (PESS) and the choice of UFs includes comments on PESS. Committee members suggested the lack of consideration to infants breastfeeding in the PBPK model (especially where cited studies have found concentrations of methylene chloride in breastmilk; Pellizzari et al., (1982)) and that an additional or larger UF may be appropriate.

- o **Recommendation 5.12:** Improve the justification for the UFs and/or changes to the UFs and consider including a database UF.

The relevance of the mouse models to humans was discussed by the Committee. The decision to base the risk assessment on mouse data was questioned, since mice have greater GSTT1 activity than rats or humans and this may make mice more susceptible to getting these types of tumors. Further information about how GST activity in mouse liver is relevant to humans is needed (research goal). More discussion is needed in the Evaluation on the relevance of mouse lung data to human health outcomes. The issue of translatability of mouse cancer data to human health outcomes is mitigated somewhat by supportive data from rats.

- o **Recommendation 5.13:** Add information on the relevance of mouse data to humans.

The inhalation-to-dermal extrapolation was discussed, and the Committee suggested the need for further clarification in the Evaluation on the basis for this extrapolation and why it was done this way. As noted by one Committee member, this calculation results in an overestimation of the dermal POD for several reasons including that dermal absorption was less complete and slower than inhalation. McDougal et al. (1986, 1990) assessed dermal absorption of vapors of several VOCs by measuring whole body penetration in rats and compared them with rats and to human dermal permeability constants. The rat constants were consistently two to four times greater than the human values. Schenk et al. (2018) recently measured the permeability coefficient and steady-state flux of 38 VOCs, including methylene chloride, for newborn pig skin in static diffusion cells.

- o **Recommendation 5.14:** Add further justification for inhalation-to-dermal extrapolation.

Additional discussion is needed regarding direct vs. indirect (i.e., systemic or blood-based)

endpoints due to the acknowledged requirement for metabolism for toxic effect. Systemic effects may be presumed to have their metabolism dominated by liver enzymes, whereas direct effects would undergo cell-type-specific metabolism, which can differ significantly from systemic metabolism or other cell-type-specific metabolisms.

One Committee member noted more explanation would be helpful for Tables 3-20. The entries in Table 3-20 (Evaluation, Section 3.2.4.2.2, pages 280-281) in the column for BMD model need to be expanded, either with footnotes or the replacement of abbreviations (i.e., spell out what the models are). To anyone not familiar with the models in benchmark dose software (BMDS), these abbreviations will be meaningless, and it is frustrating to have to search through the text or supplemental materials to determine what these are. In addition, the footnote for Table 3-20 (Evaluation, Section 3.2.4.2.2, page 281) should include how long the simulations were run (i.e., a specific length of time, or until periodicity was reached, or, etc.).

   o   **Recommendation 5.15:** Add more details to Table 3-20.

Q 5.7	**Please provide any specific suggestions or recommendations for alternative approaches that should be considered by the Agency in characterizing the chronic inhalation risks to workers**

Response:

The Committee could offer no specific suggestions or recommendation for alternative approaches for the Agency to consider in characterizing the chronic inhalation risk to workers other than those contained in the recommendations of the previous questions.

Q 5.8	**Please provide relevant data or documentation and rationale for including other studies and endpoints for consideration.**

Response:

The Committee agreed with the Agency's review of several epidemiological studies of chronic exposures to methylene chloride and their conclusion that the evidence was inconclusive for methylene chloride-induced liver toxicity and cancer. However, the lack of evidence for cancer risk in epidemiological studies is not compelling. Humans are so genetically variable, with so many other exposures and complicating issues, that it is difficult and often rare to find associations in epidemiological studies.

In the opinion of one Committee member, the inhalation unit risk values developed for this methylene chloride risk evaluation are less protective than previous dose-response assessments by EPA and OSHA, all of which relied on the same underlying data. The Evaluation should mention this, explain why new inhalation unit risks were derived and describe exactly how they differ from previous assessments. In addition, more discussion is needed to support the decision

to estimate risk using liver and lung tumors when the calculation of IUR based on mammary tumors gives the highest unit risk.

- o **Recommendation 5.16:** Model the dose responses from epidemiological studies and compare these with the dose-response models from the rodent studies to confirm HEC and IUR for chronic and cancer effects, respectively are sufficiently conservative and health protective.

- o **Recommendation 5.17:** Add rationale for not using mammary tumors as an endpoint as other evaluations have done.

The Committee noted the absence of a charge question related to potentially exposed susceptible subpopulations (PESS). The choice of UFs includes comments on PESS. Several Committee members requested additional clarification on the handling of PESS within the TSCA risk evaluation approach and especially with respect to the setting of UFs. The earlier recommendation to use a database UF was revisited with the conclusion that the Evaluation needs more explanation on why a database UF is not included.

Several Committee members suggested that UFs should account for differences among people that arise from unknown factors, and not be used to account for differences from known factors, such as GST alleles. One Committee member noted GST variation results in known subpopulations that should be taken into consideration separately, and not considered part of the general intraspecies UF.

The PBPK model does not consider breastfeeding infants (a PESS) which Committee members suggested may be an issue especially since cited studies have found concentrations of methylene chloride in breastmilk (Pellizzari et al., 1982). Many felt this is a justification for using an additional or larger UF.

- o **Recommendation 5.18:** Add more uncertainty factors (UFs) or better explain the rationale for not doing so.

EPA used a linear low-dose extrapolation for evaluating potential cancer risks from chronic exposures to methylene chloride.

Q 5.9	Please comment on the appropriateness of using a linear low-dose extrapolation versus a non-linear or threshold approach, recognizing that methylene chloride is predominantly metabolized by cytochrome P450 2E1 to carbon monoxide at low concentrations (a high affinity, low capacity pathway) and by glutathione S-transferase T1-1 to two reactive intermediates (i.e., S-(chloromethyl)glutathione) and formaldehyde) at high concentrations (a low affinity, high capacity pathway).

Response:

Different views were expressed within the Committee on likely MOA and their impact on the extrapolation model used. The Committee agreed that the Evaluation did a good job summarizing the epidemiological studies and studies in animal models for each type of cancer.

The link between methylene chloride inhalation and human liver cancer, lung cancer, breast cancer and brain cancer is inconclusive or lacking. However, animal studies reveal a clear association with liver cancer. In terms of lung cancer, there is clear evidence of a link in animals exposed via inhalation, and some evidence for oral exposure. The Committee concluded that the link to breast cancer in humans is inconclusive, although using human breast cancer as the critical outcome would lead to a lower POD. There is some evidence of a link between methylene chloride exposure and breast cancer in animals. Consequently, it made sense to use the animal data for the risk evaluation.

Several Committee members thought the mutagenic MOA was supported by studies in animal models and as a result concluded that the Evaluation is correct in using the linear low-dose extrapolation in accordance with the EPA Guidelines for Carcinogenic Risk Assessment (USEPA, 2005). Notably, studies in mice exposed to methylene chloride by inhalation found increases in chromosomal aberrations in the lung, and DNA damage in the liver, lung and peripheral lymphocytes. DNA damage in mouse and rat hepatocytes exposed to methylene chloride *in vitro* was also reported. methylene chloride was more mutagenic in *Salmonella* in the presence of GSTT1 than in the absence of GSTT1, indicating a role for a metabolite. There was no evidence of cytotoxicity or altered cell proliferation, and therefore appeared to have a non-receptor-mediated (e.g., AhR) role in cancer. Some Committee members noted the MOA for methylene chloride seems to be mutagenic involving DNA-reactive metabolites produced via GSTT1 metabolism pathway.

One Committee member noted that none of the genotoxicity studies reviewed by the Agency

were evaluated for study quality in the systematic review which prevents a valid WOE evaluation of these studies and their use in the Agency's Evaluation. In addition, there was no *in vitro* to *in vivo* exposure extrapolation provided for the *in vitro* genotoxicity studies to estimate equivalent *in vivo* exposures for genotoxicity.

- o **Recommendation 5.19:** Conduct a Data Quality Evaluation on all *in vivo* and *in vitro* genotoxicity studies included in the methylene chloride risk evaluation as described in the Application of Systematic Review in TSCA Risk Evaluations.
- o **Recommendation 5.20:** For *in vitro* genotoxicity studies, provide an *in vitro* to *in vivo* exposure extrapolation assessment to estimate equivalent *in vivo* exposures needed to produce genotoxicity based on *in vitro* genotoxicity observations.

Other Committee members thought the current WOE much more strongly supports a non-genotoxic MOA, which, if correct would lead to the use of a non-linear threshold dose-response model. These members noted that the Evaluation does not mention (consider) other potential MOAs. Some Committee members recommended including a description of the 2017 genomics and PBPK modeling work of Andersen et al., (2017). Other Committee members were less convinced by the Andersen et al. (2017) paper. The Committee noted the GST-dependent genotoxic MOA for methylene chloride was developed by Andersen and colleagues in 1987 — over 30 years ago — based on the best available evidence at that time. In their 2017 paper, Andersen and colleagues updated their MOA for methylene chloride-induced mouse tumors via a non-genotoxic MOA. One Committee member also noted that epigenetic carcinogenesis is not a separate pathway from genetic carcinogenesis, but the two often occur in the same pathway — epigenetic changes alone have not been shown to be sufficient to cause transformation, rather to "mimic" genetic changes in some steps in the multi-step carcinogenic pathway.

- o **Recommendation 5.21:** Include alternative updated MOA developed by Andersen et al. (2017) and others identified by EPA in its evaluation and through WOE evaluations provide the rationale justifying the MOA for methylene chloride-induced mouse liver- and lung-tumors.

Two Committee members noted the Agency's evaluation is incomplete due to the dose dependent mechanism being different at low-dose versus high-dose. Only when the CYP2E1 metabolism pathway becomes saturated, does methylene chloride become available for GSTT1 metabolism that produces the proposed mutagenic metabolites. The transition from CYP2E1 metabolism to GSTT1-dependent metabolism occurs at approximately 500 ppm *in vivo* (Gargas et al., 1986, Andersen et al., 1987). The issue was raised as to whether methylene chloride itself or its metabolites (or both) are causing the observed effects. The Committee recommended the Agency include discussion around these two possibilities.

One Committee member recommended the Evaluation include dose-response modeling under both the mutagenic and the non-genotoxic mechanisms, and then provide justification for the choice of model used. The whole Committee agreed that the Evaluation should include a

discussion of all likely mechanisms and provide additional rationale for the MOA on which the risk evaluation is finally based.

- o **Recommendation 5.22:** Calculate the risk from all biologically plausible MOA for methylene chloride-induced mouse liver and lung tumors.

EPA calculated a cancer slope factor by using a PBPK model that accounts for the internal dose of the amount of methylene chloride metabolized through the glutathione S-transferase T1-1 (GST) pathway.

Q 5.10	Please comment on the appropriateness of applying the PBPK model and assumptions within the model, specifically using the internal dose metric of daily mass of methylene chloride metabolized via the GST pathway as the basis for performing a linear low-dose extrapolation for quantifying potential cancer risks from chronic exposures to methylene chloride.

Response:

The Committee generally agreed with the use of the PBPK model and noted there are numerous publications showing how using PBPK models to equate internal dose metrics between species is much more appropriate than basing the risk assessment on external doses. Modeling better accounts for differences in pharmacokinetics than merely using assessment factors.

The Committee continued the MOA discussion from the previous question and concluded that the selected dose metric is appropriate given the MOA assumed in the Evaluation. Recommendations 5.21 and 5.22 suggest examination of alternate MOAs, including those discussed in Andersen et al. (2017). This may lead the Evaluation to assume a different MOA that might then require a different dose metric.

One Committee member commented on interspecies extrapolation and developing the human-equivalent dose metric and stated the Evaluation provided no reason for using the default ratio in the model.

The Committee again noted that the PBPK model does not include/assess exposure of infants through breastmilk.

- o **Recommendation 5.23:** Include models based on alternative updated MOAs developed by Andersen et al. (2017) and others applying the PBPK model and assumptions within the model, specifically using the internal dose metric of daily mass of methylene chloride metabolized into COHb per Andersen et al (2017) and other alternative MOAs identified by EPA.

Page **63** of **88**

    o **Recommendation 5.24:** Calculate the risk from all biologically plausible MOAs for methylene chloride-induced mouse liver- and lung-tumors.

Additional detailed comments

Within Section 4.3.7 page 383, of the Evaluation, the assessment of key assumptions and uncertainties in the human health risk estimation could be strengthened by including limitations in the dermal exposure assessment and uncertainty in PPE use and effectiveness.

Page 274, lines 6275-6278: EPA fails to mention that exercise increases the rates of respiration (alveolar ventilation) and cardiac output, two factors important in increasing systemic uptake of VOCs such as methylene chloride.

It is not clear whether elevated COHb levels exacerbate CNS depressant effects of methylene chloride. Neither Putz et al. (1979) nor Winneke et al. (1974) evaluated the combine effects of COHb and methylene chloride.

The Agency has not adequately addressed the topic of adverse myocardial effects of VOCs (Evaluation, page 275, lines 6294-6304). Inhalation of very high concentrations of certain VOCs can sensitize the myocardium to catecholamines, resulting in arrhythmias severe enough to be fatal. This condition is exacerbated by hypoxia. VOC levels of several thousand ppm are required to produce this effect in dogs. It is not clear whether this phenomenon is relevant to hypoxia-induced angina.

    o **Recommendation 5.25:** Further address myocardial effects.

The information presented in the Toxicokinetics (TK) section (Evaluation, pages 218 & 219) is meager. Pertinent information on interspecies differences in the metabolism and TK of methylene chloride needs to be presented, so the relevance of chronic toxicity and carcinogenicity findings in rodents to humans can be appreciated and taken into account. Green et al. (1997) reported that glutathione-S-transferase (GST) mediated biotransformation of methylene chloride is much higher in mouse than rat or human liver. Their et al. (1998) found that liver GST theta-1 activity towards methylene chloride was higher in mice than in high human conjugators, which in turn was higher than in rats, and then lower in human conjugators. Lung alveolar type II and Clara cells are believed to be the most likely the origins of methylene chloride-induced lung tumors in mice (Kanno et al., 1993). The bronchiolar Clara cell contains relatively high levels of cytochrome P4502E1 (CYP2E1) and 2F2. Thus, Clara cells metabolically activate and are disproportionately damaged by methylene chloride (Foster et al., 1994) and other VOCs (Buckpitt et al., 1995). Clara cells are much more numerous in the murine than the human lung, being distributed from the trachea to the distal bronchi of mice.

    o **Recommendation 5.26:** Add more explanation to the toxicokinetics section.

Line 5006-5007, Table 3-4: What does the "NA" designation refer to under the column headed "NOAEL/LOAEL reported by authors?" The next column does report NOAEL/LOAEL values, hence the confusion. In one case, "not reported" is stated.

One Committee member noted difficultly in identifying which papers were relied upon in the assessment of human health hazard, and the data quality ratings due to issues with citations. On page 235 the footnote indicates that Hoechst Celanese Corporation (1992) is also cited as Gibbs (1992) in EPA (2011). However, this paper is also cited as Gibbs (1992) in the DQE and in the Evaluation references section. The references section has both Hoechst and Gibbs and it is not clear if they are actually the same paper or two different papers. Hoechst is not in the DQE, but Gibbs is in the DQE as medium, which is what EPA says Hoechst was rated as. There is also a Celanase (1987) in the DQE with an unacceptable rating.

- o **Recommendation 5.27:** Be consistent with citations, including in the supplemental documents, so readers can follow which papers are being referenced and which have been evaluated for Data Quality according to the Systematic Review criteria.

- o **Recommendation 5.28:** Be consistent with citations, including in the supplemental documents, so readers can follow which papers are being referenced.

- o **Recommendation 5.29:** Add additional explanation as noted.

- o **Recommendation 5.30:** Use significant digits consistently.

Question 6: Risk Characterization:

EPA calculated environmental risk using exposure data (e.g. modeling tools and monitored datasets) and environmental toxicity information, accounting for variability within the environment. EPA concludes that methylene chloride poses a hazard to environmental aquatic receptors, with amphibians being the most sensitive taxa identified for aquatic exposures. Risk Quotients (RQs) and the number of days a concentration of concern (COC) was exceeded were used to assess environmental risks. The risk characterization section provides a discussion of the risk and uncertainties around the risk calculations.

EPA calculated human health risks for acute and chronic exposures. For non-cancer effects EPA used a margin of exposure (MOE), which is the ratio of the hazard value to the exposure to calculate human health risks. Using an acute non-cancer POD, EPA evaluated potential acute risks for workers for certain scenarios, consumer users and bystanders/non-users (e.g., children, women of childbearing age). A benchmark MOE of 30 was used with the acute POD based on CNS effects. For chronic occupational risks, EPA used a POD for liver effects as the basis of the chronic non-cancer MOE calculations. A benchmark MOE of 10 was used to interpret chronic risks for workers. An IUR for liver and lung tumors was used to evaluate potential chronic risks to cancer endpoints for the worker exposure scenarios. The risk characterization also provides a discussion of the uncertainties surrounding the risk calculations.

Q 6.1	**Please comment on the characterization of uncertainties and assumptions including whether EPA has presented a clear explanation of underlying assumptions, accurate contextualization of uncertainties and, as appropriate, the probabilities associated with both optimistic and pessimistic projections, including best-case and worst-case scenarios.**

Response:

The Committee agreed that in general the Agency has done a decent job at describing the assumptions underlying most of the derivations and calculations in the Evaluation, as well as providing the rationale for choosing to use one data source versus another or using one set of estimates versus another. In Table 4.3 (Evaluation, page 320) the sources of uncertainty for every aspect of the Evaluation were quite thoroughly discussed, from the exposure assessment component and the estimation of methylene chloride concentration in water to the sources of uncertainties that undermine the workers and consumer exposure assessment, up to the human health risk estimation. However, one Committee member noted that in its review of the resulting risk estimate for chronic exposure of ONU for two scenarios (repackaging and plastic and rubber product manufacturing), the Evaluation reports: "... In consideration of the uncertainties in the exposures for ONUs for this COU, EPA has determined the non-cancer risks presented by

chronic inhalation are not unreasonable" (p 432 and 436).

The justification for this statement is the use of the pre-1997 updated OSHA PEL exposure data. This justification seems arbitrary, given that pre-1997 data was used to estimate exposure for fabric finishing and spot cleaning. Since the Evaluation establishes the need and utility of the pre-1997 data in one case, it should also use all the data for repackaging and plastic and rubber product manufacturing. Alternatively, the Evaluation should explicitly state under what conditions data do not represent exposure (or hold too much uncertainty) prior to the risk determination stage.

o **Recommendation 6.1:** Be more explicit and consistent with respect to what data is deemed usable for the determination of exposure and risk.

The Committee provided suggestions regarding different procedures that could be used to derive risk projections for workers. One Committee member suggested use of the personal air sampling data employed in the Evaluation, the use of a higher level for personal exposures in the occupational exposure assessment, and that new results be compared to the POD. Two Committee members suggested that EPA use the OSHA inspection database to obtain sample data, and that actual samples from the database are used rather than fixing certain parameters to fixed percentiles in the parameter distribution.

Finally, one Committee member invited the Agency to use a Monte Carlo approach to ensure that variability and uncertainty are handled within one consistent framework as discussed in the EPA guidance document (EPA, 1997): according to the Committee member, the Evaluation displayed a lack of consistency in addressing both. To achieve this, the Committee member suggested that EPA use a probabilistic approach in the risk calculation derivation by providing each parameter (including fate properties, amount of methylene chloride discharged directly or indirectly in water sources, number of facilities that use or discharge methylene chloride, frequency of release, APF, extent of use of PPE, and the UF used) with distributions derived from previous studies, rather than using a mixed approach where certain parameters are kept fixed, while others are sampled from uniform distributions with ranges derived from the literature. The Committee member also commented that by using a Monte Carlo approach, it would be easier to make probability statement regarding both optimistic and pessimistic projections, which the Committee member believed were hard to quantify directly from the Evaluation.

During Committee deliberations, concerns were expressed multiple time with the way the Evaluation handles the issue of respirator and use of personal gloves use as factors modifying human health risk from methylene chloride exposures. In sections 4.3.2 and 4.3.7 of the Evaluation, where the key assumptions and uncertainties of the occupational exposure assessment are discussed, the assumptions and uncertainties with regard to respirator use and the assumed protection are not discussed. When COU scenarios are discussed, the best-case scenarios assume workers optimally and properly employ PPE, typically appropriate gloves, for personal protection. However, since methylene chloride can penetrate gloves over the time of use, best industrial hygiene practice guidelines necessitates that workers change the gloves

frequently during their 8-hour working period. In general, this discussion left some Committee members unclear as to how PPE use is actually factored into the human health risk calculations.

See the discussion for Question 4.1 for references to other data sources that can be tapped to obtain potentially more realistic estimates of PPE use.

As a result of this discussion, the Committee recommended the following:

- o **Recommendation 6.2:** Add the use of respirator and personal gloves as both a key assumption and as a source of uncertainty.

- o **Recommendation 6.3:** Acknowledge that workers do not wear gloves continuously over their work shift and incorporate this assumption into calculations of risk for certain categories of workers.

- o **Recommendation 6.4:** Discuss more thoroughly all the assumptions made with respect to respirator use and its protective effect.

Finally, changes in wording as well as more clarifications regarding some procedures used by the Agency were requested.

One Committee member urged that in the Evaluation, the expression *"no risk"* be replaced always with the expression *"no unacceptable risk"* in recognition of the inherent variability and estimator uncertainty associated with assessing even low-risk scenarios. We can never be certain that the true risk is zero.

- o **Recommendation 6.5:** Refrain from using the expression "no risk" and use instead the expression "no unacceptable risk" in light of all the uncertainty and variability that surround all the estimates.

Another Committee member asked for additional clarification of the statement in page 383 of the Evaluation:

"... Because of this the results of risk characterization were generally not sensitive to the individual estimates of the central tendency and high-end separately but rather were based on considering both central tendency and high-end exposure which increase the overall confidence in the risk characterization."

This statement suggests that considering the risks from central tendency and the high-end exposures separately somehow increases confidence in results.

- o **Recommendation 6.6:** Be more transparent with respect to the decision of using estimates of central tendency and high-end jointly as a way to increase confidence in the risk characterization.

Q 6.2	**Please provide information on additional uncertainties and assumptions that EPA has not adequately presented.**

Response:

As already elaborated upon in the response to Charge Question 6.1, the Evaluation does a decent job of characterizing the uncertainties surrounding many of the parameters and model inputs that contribute to the risk characterization.

The Committee identified the following issues/assumptions that represent sources of uncertainty not currently addressed in the Evaluation. None of these topics received extensive elaboration.

Effects of simultaneous dermal and inhalation exposures: Inhalation and dermal exposure to methylene chloride can occur simultaneously. Are effects simply additive (an undiscussed assumption)?

Data Gap – data on the effect of long-term repeated exposures: In particular, the Committee expressed concern that long-term repeated inhalation exposures to methylene chloride can lead to other respiratory illnesses, such as asthma, which has been reported with long-term exposures to VOCs in general.

Data Gap – data on neurotoxicity on outcomes such as CNS depression and cognitive deficits: The Committee has discussed the need for data on neurotoxicity in the context of other chemical evaluations it has reviewed.

Uncertainty in the definition of what constitutes a chronic exposure to animal species: Typically, chronic exposures are those that span more than 10% of an organism's life span. As *ambystomid* salamanders can live over 25 years in captivity, a chronic exposure for them would last over 2.5 years. Thus, a nine-day exposure for these organisms is subacute or simply a repeated dose, borderline sub-chronic exposure at best, and definitely does not represent a chronic exposure. Even though mortality was assessed (or inferred based on significant terata), the Evaluation in Table 3.2 (Evaluation, page 213) assigns an AF of 10 when summarizing environmental hazards for amphibians. This seems to be consistent with the opinion of the study authors regarding adverse reproductive impairment. The Evaluation should present an acute-to-chronic estimate calculated using the ACE tool in order to provide corroborative evidence in support of the AF proposed. (Note: the genus of frogs identified as *Rana* in the Evaluation is now *Lithobates*.)

Uncertainty in water releases: The uncertainty in downstream values of methylene chloride used in the water release assessment should be addressed in the Evaluation.

Q 6.3	Please comment on whether the information presented supports the findings outlined in the draft risk characterization section.

Response:

The Committee agreed that in general the Evaluation has adequately presented the information that supports the findings outlined in the draft risk characterization section, and the findings outlined in the risk characterization section are consistent with the numerical results.

- o **Recommendation 6.7:** To aid readability, present findings (e.g., "Risk Conclusion" in Section 4.6) at the beginning of the Risk Characterization section rather than at the end.

Several Committee members commented on specific aspects of the risk characterization findings.

One Committee member noted that five out of 21 (23.8%) manufacturing facilities examined in the assessment were found to pose an unreasonable risk. Given that in 2019 there were 81,654 facilities reporting disposal of methylene chloride, it is quite possible that many these facilities, if examined, would also be found to pose an unreasonable risk. This admittedly simplistic extrapolation suggest that methylene chloride releases pose an unreasonable risk for environmental/aquatic receptors simply because of the large numbers and geographical spread of manufacturing facility releases. EPA should acknowledge the implications of this extrapolation in its environmental risk characterization.

Two Committee members remarked that very likely the Agency has not accounted for all sources of uncertainty and variability (such as e.g. GST polymorphisms, data base uncertainty factors), and, that as a result, conclusions on risk characterization were fraught with lingering uncertainties.

One Committee member suggested that very likely the Evaluation underestimates risk during the process of risk characterization. In the opinion of this member, the target MOEs were not sufficiently large to capture the uncertainties in the assessment (such as e.g., GST polymorphisms, data base UFs) and thus conclusions of no unreasonable risk, for example for ONUs, cannot be adequately supported. In the spirit of protecting public health, the Committee member invited the Agency to acknowledge the unaccounted sources of uncertainty and as a result include more scenarios in the unreasonable risk category. This move is critical since future risk management actions are likely to focus on reducing uncertainty and risk specifically in those scenarios identified with unreasonable risks.

One Committee member stated that the many lingering uncertainties still pervasive in many aspects of the exposure assessment and the risk characterization make it impossible to reach robust conclusions on risk characterization. In several parts of the Evaluation, the possibility of both overestimation and underestimation are discussed. This Committee member cautions that overestimation in one part of the risk characterization calculation and underestimation in another part do not cancel each other out. The two errors are not the same and do not carry the same weight in terms of human health risk assessment. The Committee members observed that

increased monitoring efforts, both in terms of occupational exposure and environmental monitoring, coupled with a more unified probabilistic approach for risk assessment — particularly a Bayesian framework — could help reduce some of the uncertainties still persisting and can help reach more conclusive statements regarding human health risks.

Q 6.4	Please comment on the objectivity of the underlying data used to support the risk characterization and the sensitivity of the Agency's conclusions to analytic assumptions made.

Response:

As the method used to derive the quantities that are used to characterize risk (the margin of exposure and the risk quotients), build upon estimates obtained in the previous Chapters of the Evaluation, the suggestions and recommendations that the Committee set forth when answering previous charge questions also apply here.

In terms of analytical assumptions, while overall the Evaluation provides reasonable explanations as for the assumptions made, two additional items that the Committee particularly emphasized were:

(i)   In estimating environmental risk, the Agency should alter the input parameters of the Probabilistic Dilution Model (PDM) of E-FAST, or alternatively consider using a more robust model to better reproduce concentrations observed downstream of the manufacturing facilities.

(ii)   Inhalation and dermal exposures from chemicals, and especially volatile chemicals like methylene chloride, are not considered jointly in assessing health risks to workers and consumers (see discussion Section 6.2). This represents an unresolved source of uncertainty that should be addressed in future risk assessments.

The EPA characterization of human health risk from inhalation exposure to workers includes estimates of risk for respirator use. These estimates are calculated by multiplying the high end and central tendency MOE or extra cancer risk estimates without respirator use by the respirator assigned protection factors (APFs) of 25 and 50 (air-supplied respirators). EPA did not assume ONUs or consumers used personal protective equipment in the risk estimation process.

Q 6.5	Please comment on whether EPA has adequately, clearly, and appropriately presented the reasoning, approach, assumptions, and uncertainties for characterizing risk to workers using air-supplied respirators and to ONUs and consumers who would not be expected to use PPE.

Response:

Calculation of human health risk from inhalation is derived — as for any human health non-cancer risk due to acute exposure or chronic exposure — from hazard values and human exposure. As such, the same comments and suggestions regarding the appropriateness of assumptions provided in response to previous Charge Questions (in particular Charge question 5.6) with respect to characterization of human health hazard are valid in this context.

With respect to assumptions regarding the use of air-supplied respirators and PPE, the Committee expressed various concerns. Several Committee members questioned the use of APFs to indicate protectiveness of PPE, and others noted that the actual use of PPE as well as the proper use of PPE in affected occupations had not been sufficiently investigated.

Committee members indicated that discussion of PPE use in the Evaluation did not address known factors that affect workers' or ONUs' use of PPE, such as discomfort, limitations in movement, sensory perception (i.e., hearing, vision, touch). These factors are exacerbated as task-time and temperature increase, implying that even under the best-case scenario of proper use of PPE at the beginning of a work shift, use of PPE will degrade over time, both within a daily work shift and over the course of a worker's career because of increasing reluctance to use PPE.

The Committee suggested that there is variability in use of PPE across manufacturing facilities, with larger and better-funded manufacturing industries and facilities often having industrial hygiene compliance programs. However, although for some COUs PPE use is needed and required, PPE use might not be the case always and everywhere, and large uncertainties exist as for the actual use of PPE across multiple industrial sectors. The Committee encouraged EPA to look for existing literature on PPE use for a more evidence-based approach when characterizing uncertainty regarding PPE use.

One Committee member thought that PPE use should not be considered when determining risk. Rather, it should be considered only in a risk management phase, except for COUs where EPA

ascertains the proper use of PPE and other exposure controls at least 95% of the time. This Committee member believed that EPA should consider any scenarios that present unreasonable risks without assuming PPE use, while the risk management process should be focused on designing and ensuring appropriate PPE use and other controls.

Some Committee members also offered comments, albeit contrasting, about risk estimates summarized in Table 4-104 (Evaluation, pages 395-410), where hazard characterization for all conditions of use with and without PPE are reported. Some Committee members appreciated that the Table presented an evaluation of human health risk without the use of PPE and its reduction due to PPE use, and found the table to be effective in communicating results. Other Committee members felt that the table was too detailed to navigate easily. These Committee members offered recommendations for developing an easier-to-read table. One suggestion was that the Table shows results only for 3 categories: no unreasonable risk, no unreasonable risk under condition of proper PPE use, and unreasonable risk even under conditions of proper PPE use.

Question 7: Overall Content and Organization:

EPA's Final Rule, Procedures for Chemical Risk Evaluation Under the Amended Toxic Substances Control Act (82 FR 33726) stipulates the process by which EPA is to complete risk evaluations under the Frank R. Lautenberg Chemical Safety for the 21st Century Act.

As part of this draft risk evaluation for methylene chloride, EPA evaluated potential environmental, occupational and consumer exposures. The evaluation considered reasonably available information, including manufacture, use, and release information, and physical-chemical characteristics. It is important that the information presented in the risk evaluation and accompanying documents is clear and concise and describes the process in a scientifically credible manner.

Q 7.1	**Please comment on the overall quality and relevance of the resources used in this draft risk evaluation; describe data sources or models that could improve the risk evaluation.**

Q 7.2	**Please comment on the overall content, organization, and presentation of the draft risk evaluation of methylene chloride.**

Q 7.3	**Please provide suggestions for improving the clarity of the information presented in the documents.**

Response:

Organization and Clarity

These Draft Risk Evaluations clearly show continued improvement in organization and clarity as EPA staff strive to incorporate lessons from the SACC's input on earlier draft risk evaluations. Navigation was more difficult with this Evaluation compared to previous ones, but this may reflect the sheer size of the Evaluation and supplemental documents. Committee members offered different ideas about what would make the document easier to understand. Some wanted the document to stand alone and be understandable without referring to externally linked documents, by concisely summarizing the information taken from the external document. Others asked for more links to external supporting materials to improve readability and shorten this document. Many on the Committee asked that links to external documents that support specific decisions or parameters should be made more specific (e.g. to a specific page number in the external document) and also that the Evaluation include concise summaries of parameters or decisions that are based on external documents.

While in some cases EPA's choices are explained, many on the Committee asked for more clarity about rationale for the many choices that influence the risk evaluation, and clearer presentation of assumptions.

Committee members requested clearer presentation of risk characterization findings that show whether the condition of use results in "no unreasonable risk" or "unreasonable risk" for each condition evaluated both with and without PPE use.

Detailed Response

Relevance and quality of data sources

Conceptual model and completeness of the assessment: Committee members commented that the document did not include adequate information to assess whether the conceptual model captured all the important conditions of use and opportunities for exposure. A mass balance analysis is suggested to describe the disposition of all the methylene chloride produced or imported to its ultimate disposal, in order to assure the risk evaluation addresses all major exposure opportunities. The Agency may need to collect data to close data gaps that currently limit the ability to carry out such an analysis. Figure 1-1 (Evaluation, page 44) was described as helpful by one Committee member, who also asked whether it could be merged with more COUs and an overall mass balance approach.

Several Committee members expressed concern that large quantities of methylene chloride are volatilized to ambient air from diverse and disperse uses and that there is no COU that provides a basis for setting any limit on these emissions. While EPA asserts that the Clean Air Act (CAA) can be used to control these emissions, Committee members thought the CAA would address only a fraction of total emissions, i.e. only from Major Sources as defined by the 1990 CAA Amendments. Several Committee members also suggested that the impact of methylene chloride emissions on ozone depletion as an endpoint should also be considered in the Evaluation.

In a related issue, some Committee members were concerned that EPA did not have adequate methylene chloride production use and discharge data and had to rely on industry data — for example from market reports. They were concerned that market reports and other industry data have not been evaluated for quality, for example: "In 2005, the use percentages of methylene chloride by sector were as follows: paint stripping and removal (30%), adhesives (22%), pharmaceuticals (11%), metal cleaning (8%), aerosols (8%), chemical processing (8%), flexible polyurethane foam (5%), and miscellaneous (8%) (ICIS, 2004)." (Evaluation, page 40)

Regulatory coverages and gaps: A short summary of methylene chloride's regulatory status under EPA, OSHA, and FDA should be included and would be more helpful to evaluate the conceptual model and completeness of the risk evaluation than just being directed to the appendices with the lists of regulations.

Dose response assessment: Committee members suggested that EPA clarify where dose-response values derived for this assessment are substantially different from previous assessments by EPA, and perhaps to explain why a new assessment was conducted. While Table 1-3

(Evaluation, pages 41-42) lists previous assessments, it would be more helpful to indicate which of these are foundational for the current risk evaluation. In fact, on page 38, the Evaluation says readers should look at this in an integrated way: "As EPA explained in the Risk Evaluation Rule (82 FR 33726 (July 20, 2017)), it is important for peer reviewers to consider how the underlying risk evaluation analyses fit together to produce an integrated risk characterization, which forms the basis of an unreasonable risk determination."

With respect to the previous two comments, Section 3.1.3 of the Evaluation provides a good example of criteria and scope for the ecological risk evaluation. For example, the document describes useful criteria from other EPA analyses instead of just citing the previous document from 1998 and expecting readers to find the relevant information.

> "EPA determined that data and information were relevant based on whether it had biological, physical-chemical, and environmental relevance (EPA, 1998):
> - Biological relevance: correspondence among the taxa, life stages, and processes measured or observed and the assessment endpoint.
> - Physical-chemical relevance: correspondence between the chemical or physical agent tested and the chemical or physical agent constituting the stressor of concern.
> - Environmental relevance: correspondence between test conditions and conditions in the environment (EPA, 1998)."

One Committee member commented that the first mention of the new rule on methylene chloride in residential paint strippers in Section 1.4.1 appears too late in the Evaluation. Also, the text in this paragraph has descriptions of COUs that are not consistent within the problem formulation.

One Committee member suggested including Globally Harmonized System (GHS) classification information on the subject chemical.

Committee members discussed the need to add representatives from OSHA and/or NIOSH to the SACC since many of the COUs are worker exposures.

One Committee member suggested that it would be useful to use links in the tables (including footnotes) so it would be easy to go from say, an estimate provided in a table to the section where the estimate was derived. Another suggested EPA could provide improved links between spreadsheets. With respect to improving ability to reproduce calculations, a Committee member stated it would be helpful to provide more descriptive information about where to look specifically in references or in model user documentation for the critical information necessary to reproduce a calculation.

Committee members suggested EPA standardize first- and second-level headings for the risk evaluations and suggested providing a subsection at beginning of each section to summarize findings in that section. The headings in the human hazard section are not clear or logical to follow.

Committee members also suggested that additional summary graphics (e.g., concept maps, bar charts) would allow readers to quickly grasp the big picture.

Committee members requested clearer presentation of risk characterization findings that show whether the condition of use results in "no unreasonable risk" or "unreasonable risk" for each condition evaluated both with and without PPE use.

One Committee member commented that EPA's description of the WOE determination for carcinogenicity was clearly described.

One Committee member suggested that a table of risk characterization conclusions at the beginning of that section would be helpful. Others pointed to the list of scenarios in the Executive Summary as a helpful outline of what could be presented in the risk characterization.

A Committee member suggested organizing the report to present information about consumer exposure for each COU and after that to present information about bystander exposure for each consumer COU.

While in some cases EPA's choices are explained, many on the Committee asked for more clarity about rationale for the choices, and clearer presentation of assumptions. For example, for the variables chosen for PBPK modeling, it would be helpful to provide a brief explanation of how each variable was chosen instead of referring to other documents. Many on the Committee asked that the Draft Risk Evaluation include concise summaries of parameters or decisions that are based on external documents.

Committee members praised the clarity of the OPPT Technical Presentation and suggested it could be included in future virtual pre-meetings, and in the risk evaluation as a summary.

- o **Recommendation 7.1:** Add conclusion sentences to be helpful in synthesizing data.
- o **Recommendation 7.2:** A mass balance analysis is suggested to describe the disposition of all the methylene chloride produced or imported to its ultimate disposal, in order to ensure the risk evaluation addresses all major exposure opportunities.
- o **Recommendation 7.3:** The impact of methylene chloride emissions to the ambient air, including population exposures living in close proximity to large and small emission sources of methylene chloride. These populations can be considered potentially exposed subpopulations in the context of PESS.
- o **Recommendation 7.4:** The impact of methylene chloride emissions to the atmosphere on ozone depletion as an endpoint should also be considered in the Evaluation.
- o **Recommendation 7.5:** Committee members requested clearer presentation of risk characterization findings that show whether the conditions of use result in "no

unreasonable risk" or "unreasonable risk" for each condition evaluated both with and without PPE use.

o **Recommendation 7.6:** A short summary of methylene chloride's regulatory status under EPA, OSHA, and FDA should be included and would be more helpful to evaluate the conceptual model and completeness of the risk evaluation than just being directed to the appendices with the lists of regulations.

o **Recommendation 7.7:** Committee members suggested that EPA clarify where dose-response values derived for this assessment are substantially different from previous assessments by EPA, and perhaps explain why a new assessment was conducted.

o **Recommendation 7.8:** Committee members requested more clarity about rationale for the many choices that influence the risk evaluation, and clearer presentation of assumptions.

o **Recommendation 7.9:** Links to external documents that support specific decisions or parameters should be made more specific (e.g. to a specific page number) and also the risk evaluation should include concise summaries of parameters or decisions that are based on external documents.

o **Recommendation 7.10:** Provide more descriptive information about where to look specifically in references or in model user documentation for the critical information necessary to reproduce a calculation.

o **Recommendation 7.11:** Committee members suggested EPA standardize first-level and second-level headings for the risk evaluations and suggested providing a subsection at beginning of each section to summarize that section.

o **Recommendation 7.12:** Consider including Globally Harmonized System (GHS) classification information on the subject chemical.

o **Recommendation 7.13:** Consider adding representatives from OSHA and/or NIOSH to the SACC.

o **Recommendation 7.14:** Numerous tables in the Evaluation are not consistent with using two significant digits.

Typos and editorial suggestions
- Committee members reported that there were broken links in some places.

- Line 46: specify that total aggregate production volume 2012-2015 is 230-264 million pounds *per year*.

- Table 5-1 is difficult to understand

- In the References section some EPA references are under EPA, U.S. and others are under U.S.EPA. Suggest EPA pick one format and stick with it.

- An error was noted at line 3997 (Evaluation, page 198) where the word "faction" relating to absorbed dose should be "fraction."

- Remove "simply" from lines 246 and 6893 (or replace with simple)

- Change "estimate" to "estimated" line 273

- Not sure if page 43 was intentionally left blank or if the page didn't load correctly

- Lines 4593 and 4595 need to have reference formats corrected surrounding the Stewart et al. 1976 reference.

- The sentence on lines 4687-4690 does not make sense because studies were evaluated in a qualitative manner, and a dose-response assessment for acute was not possible because the study chosen was a single dose.

- If referring to an evaluation from a different program at EPA, like IRIS, the reference would be clearer if it indicated EPA IRIS assessment. For example, this reference on line 6163 is confusing: "EPA is relying on the dose-response modeling results presented in U.S.EPA (2011) from Nitschke (1988a) for rats." This is confusing the use of EPA and U.S. EPA. Some places, IRIS assessment is referenced, and it is much clearer, like on line 6185.

- Lines 6195 and 6196 are repetitive to line 6184 unnecessarily.

- Putz is sometimes referenced as Putz (1979) and other times as Putz et al. (1979). Should be consistent.

- Line 6244 need to correct reference format. Also, the NAC/AEGL reference is provided and AEGL used the PBPK model according to the uncertainties section (line 9133) - and AEGL2000 figure 3 (The methylene chloride concentrations for the AEGL-2 exposure times from 10 min to 8 hours were thus derived with the PBPK-model for both endpoints)

- EPA 1980 on line 6345 does not link to the correct reference (it links to the Effects of Organic Compounds on Amphibian Reproduction) and does not support the conclusions in this paragraph.

- Line 6451 "based on" would be a better choice than "from" because NTP doesn't derive IURs.

- Line 6849 reference hyperlinks need correcting. Also, this references the RfD/RfC guidance that includes database UFs. If there is different guidance indicating that database UFs are not used in this analysis, that should be cited.

- Numerous tables are not consistent with using 2 significant digits

- Section 2.4.1.1 – pg 110 – Eq. 2-7 – this equation is different than the one given in the supplemental material for this section (Supplemental Information on Releases and Occupational Exposure Assessment, Section 3.2, page 113) and the Committee believes the one in the supplemental material is the one actually used for the calculations. The Committee also recommended mentioning the possible values of Fabs when defining this parameter in the text as is done with some of the other parameter values

- Sections 2.4.1.2.5, 2.4.1.2.6 and 2.4.1.2.8 – pages 123, 125 and 129 – The text states that Monte Carlo simulation was done but it does not state that Latin Hypercube sampling (LHS) was done. It does state in the supplemental material that LHS was done, but it should say that in the main text as well as in the supplemental material.

- Pg 128 and 150 – Tables 2-46 and 2-70 – The Committee could not duplicate these calculations (we calculated 97 and 290 whereas the tables had values of 94 and 280) – these may be due to rounding in the calculations, but they should be double checked to be sure

- Section 2.4.1.2.11 – pg 137 – typo in high-end value – should be 3,000 instead of 3,00

- Table 2-57, page 138 –the value for Yderm in this table is should be 0.9 (as in Table 2-85, pg 165 for this worker category) instead of 1.0

- Section 2.4.1.2.13 – page 142 – line 2822 – uses "representative" when it should be "representativeness" – noticed some other instances of this as well

- Section 2.4.1.2.16 – page 147 – line 2949 –something is missing from the sentence

- Section 2.4.1.3 – Table 2-84 – pages 163-164 – There are numerous places where entries do not match with the entries in the corresponding individual tables. Additionally, in some of the lower rows on page 163 and all but the last row on page 164, the values in the columns for Central Tendency and High End need to be shifted down a row.

- Section 2.4.2.4.15 – pg 193 – line 3900 – Text says "six scenarios" but should it be three?

- Supplemental document on Releases and Occupational Exposure Assessment

  o Section 1.3 – page 22 – Section XX? The "XX" was supposed to be replaced.

  o Section 3.2 – Table 3.3 – page 118 –it would be useful to have the values for Fabs in this table.

- Appendix D – page 253 – The text references Appendix B, but it cannot be Appendix B of this document (based on title and content of Appendix B in this document).

- Appendix E – E.6 – pg 261 – The text references parameter "M" in Eq. E-10, but there is no "M" in E-10.

- Appendix F – F.1.1 – page 266 – Eq. F.1-15 –recommend putting in text describing this equation what the value of 0.0833 is.

- Appendix F – page 269 – Table Apx F-1 – a lower bound for the near-field indoor wind speed of 8.78 cm/s is shown in the table, but the text describing this parameter (page 272) gives a value of 202.2 cm/s.

- Appendix F – page 270 – Table Apx F.1 – the table does not show a distribution for NJ (number of brake jobs per work shift). From reading the text, it seems that perhaps a discrete distribution may have been used. If this is the case, the table should be updated.

- Appendix F – F.2.1 – page 279 – The references in the text to equation numbers is wrong. The third line on this page says: "Equation F.1-19 below," but the equation below is F.2-38. Same for the other 2 equations on this page.

- Appendix F – page 280 – Table Apx F-3 – a lower bound for the vapor generation rate of 0.015 is given, but the text describing this parameter (pg 285) gives a value of 0.02.

- Appendix F – page 280 – Table Apx F-3 – a distribution isn't given for this parameter

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